

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



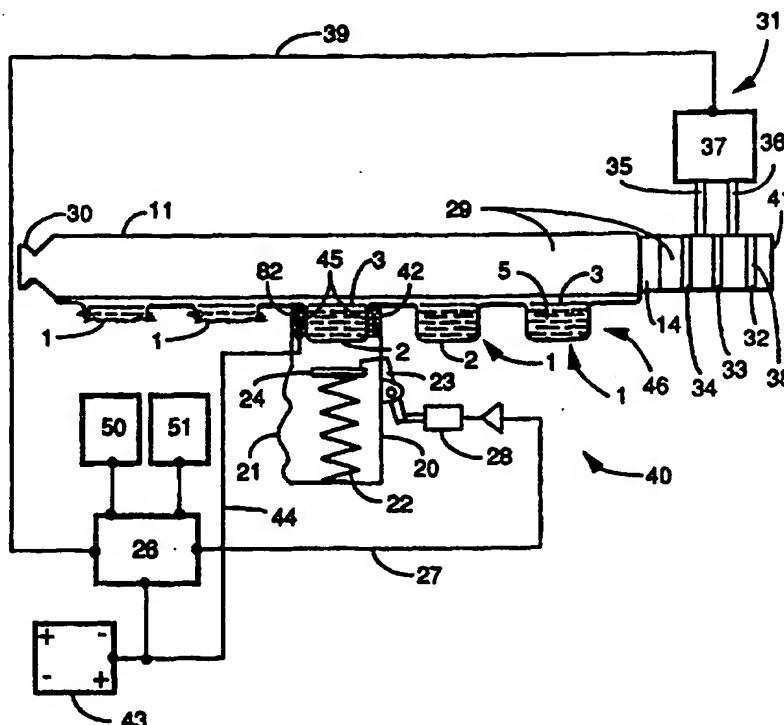
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : <b>A61M 11/00, 15/00, B65D 47/10</b>		<b>A1</b>	(11) International Publication Number: <b>WO 96/13290</b>
			(43) International Publication Date: <b>9 May 1996 (09.05.96)</b>
(21) International Application Number: <b>PCT/US95/13872</b>		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, LS, MW, SD, SZ, UG).	
(22) International Filing Date: <b>27 October 1995 (27.10.95)</b>			
(30) Priority Data: <b>08/330,971</b> <b>28 October 1994 (28.10.94)</b> <b>US</b>			
(71) Applicant: <b>ARADIGM CORPORATION [US/US]; 26219 Eden Landing Road, Hayward, CA 94545 (US).</b>			
(72) Inventors: <b>LLOYD, Lester, J.; 7 Haciendas Road, Orinda, CA 94563 (US). LLOYD, Peter, M.; 6239 Elderberry Drive, Oakland, CA 94611 (US). RUBSAMEN, Reid, M.; 102 El Camino Real, Berkeley, CA 94705 (US). SCHUSTER, Jeffrey, A.; 5 El Portal Court, Berkeley, CA 94708 (US).</b>			
(74) Agent: <b>BOZICEVIC, Karl; Fish &amp; Richardson P.C., Suite 100, 2200 Sand Hill Road, Menlo Park, CA 94025 (US).</b>			
		<b>Published</b> <i>With international search report.</i>	

(54) Title: **DEVICE FOR AEROSOLIZED DELIVERY OF PEPTIDE DRUGS**

(57) Abstract

A method of treating human patients is provided by the intrapulmonary delivery of a pharmaceutically active peptide formulation (5). The formulation is automatically released in an aerosolized form from a hand-held, self-contained, portable device (40) comprised of a means (23) for automatically releasing a measured amount of drug into the inspiratory flow path (29) of a patient in response to information obtained from a means (37) for measuring the inspiratory flow rate and determining the inspiratory volume of a patient. Reproducible dosing is obtained by providing for automatic release at the same inspiratory flow rate and inspiratory volume each time drug is released. The device includes a timer to enable a patient to take a drug at the same time each day. Further, overadministration of hormone formulation is avoided by providing a pre-programmed microprocessor (26) designed to avoid overdosing.



BEST AVAILABLE COPY

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LV	Latvia	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
CZ	Czech Republic	MD	Republic of Moldova	TJ	Tajikistan
DE	Germany	MG	Madagascar	TT	Trinidad and Tobago
DK	Denmark	ML	Mali	UA	Ukraine
ES	Spain	MN	Mongolia	US	United States of America
FI	Finland			UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

- 1 -

DEVICE FOR AEROSOLIZED DELIVERY OF PEPTIDE DRUGSField of the Invention

5           This invention relates generally to devices, containers and methods for administering peptide hormones for endocrine therapy. More specifically, this invention relates to devices, containers and methods for the delivery of peptide hormone drugs wherein the device is a hand-held, self-contained device which automatically and repeatedly releases a controlled amount of peptide drug to a patient at the same point in the respiratory cycle of the patient based on a range of different criteria which are simultaneously considered so as to obtain a high degree of repeatability in dosing.

Background of the Invention

Potent peptide hormones are available for a variety of therapeutic indications. Leuprolide, for example, is a GnRH super-agonist useful in the treatment of endometriosis and prostrate cancer. Leuprolide also has potential applications in the field of breast cancer management and the treatment of precocious puberty. Calcitonin enhances metabolism and may be a useful therapeutic agent for the management of osteoporosis, a common complication of aging.

25           To treat conditions or diseases of the endocrine system, pharmaceutical formulations containing potent peptide hormones are typically administered by injection. Because the stomach presents a highly acidic environment, oral preparations of peptides are unstable and readily hydrolyzed in the gastric environment. Currently, there are no oral preparations of therapeutic peptide agents available.

Both calcitonin and leuprolide can be administered nasally. (See Rizzato et al., Curr. Ther. Res. 45:761-766,

- 2 -

1989.) Both drugs achieve blood levels when introduced into the nose from an aerosol spray device. However, experiments by Adjei et al. have shown that the bioavailability of leuprolide when administered intranasally is relatively low. Adjei and Garren, Pharmaceutical Research, Vol. 7, No. 6, 1990.

An increase in the bioavailability of leuprolide can be obtained by administering the drug into the lung. Intrapulmonary administration of leuprolide has been shown to be an effective means of non-invasive administration of this drug. Adjei and Garren, Pharmaceutical Research, Vol. 7, No. 6, 1990. Intrapulmonary administration of leuprolide and other peptide drugs has the additional advantage of utilizing the large surface area available for drug absorption presented by lung tissue. This large surface area means that a relatively small amount of drug comes into contact with each square centimeter of lung parenchyma. This fact reduces the potential for tissue irritation by the drug and drug formulation. Local irritation has been seen with nasal delivery of insulin and has been a problem for commercialization of nasal preparations of that drug.

- 3 -

It is a problem with peptide hormones that they are very potent with effects that are not immediately manifested. For example, therapy with leuprolide for prostate cancer does not typically produce any acute clinical effects. Similarly, prophylaxis against osteoporosis with calcitonin will not produce any acute symptoms discernible to the patient. Therefore, administration of each dose of these drugs must be reliable and reproducible. In addition, careful compliance monitoring is important to avoid therapeutic failures by carefully following the patient's adherence to the prescribed dosing regiment.

In addition, because these drugs are potent therapeutic agents, care must be taken to avoid overdosing. The most convenient form for intrapulmonary administration of drugs by ambulatory patients is through the use of a metered dose inhaler. Metered dose inhaler devices allow the self-administration of a metered bolus of drug when the device is manually actuated by the patient during inspiration. However, such devices must be used with the proper inspiratory maneuver in order to promote effective deposition of the drug into the lung. In addition to performing a correct inspiratory maneuver, the patient must self-actuate the metered dose inhaler during the appropriate part of the inspiratory cycle. Further, when using such devices, it is not typically self-evident to the patient that the drug was properly or improperly administered. For those drugs without immediate clinical effect, the patient can easily misuse the metered dose inhaler and be under the false impression that he is correctly self-administering the drug as prescribed. Similarly, the patient may be under the false impression that he performed an incorrect inspiratory maneuver in metered dose inhaler actuation when he in fact properly

- 4 -

performed these operations and received an appropriate amount of drug.

Devices exist to deliver metered dose inhaler drugs into the lung in a breath-actuated manner. However, such  
5 devices do not measure inspiratory flow rate and determine inspiratory volume in order to trigger the device. Therefore, a sub-optimal inspiratory maneuver (e.g. one with too high of an inspiratory rate) could be used to actuate the device and produce a sub-optimal deposition  
10 pattern of drug into the lungs resulting in a sub-therapeutic blood level of the therapeutic agent being delivered. If delivery took place at the correct point in the inspiratory cycle the dose delivered would be high -- overall dosing would be erratic in that drug is released at  
15 different points in the inspiratory cycle.

When using a metered dose inhaler, the dosing events must be manually recorded by the patient. Many potent therapeutic hormone peptide drugs are given only once a day. It is important that the patient remember to take the  
20 prescribed daily dose, and that the dose be taken at the correct time of the day. Further, it is important that the patient not take more than the prescribed number of doses per day. The timing of delivery of potent therapeutic hormone peptide drugs is critical because these drugs  
25 interact intimately with the chronobiology of the patient's physiology in order to produce their desired effect.

When using standard metered dose inhaler devices, the patient must manually record the time of each dosing administration. In addition, the patient must remember  
30 when to self-administer the drug. Devices exist for recording automatically metered dose inhaler drug delivery events. However, such devices do not record the presence of inspiratory flow at the time of device firing. This means that a noncompliant patient can fire the metered dose  
35 inhaler into the air and have a valid drug dosing event

- 5 -

recorded on the self-containing recording means. In addition, the patient could self-administer the drug with an inappropriate inspiratory maneuver and have a valid drug dosing event recorded by the device. This would lead the physician to assume that the patient was compliant when he was receiving an inappropriate amount of drug with each dosing event.

#### Summary of the Invention

Devices, packaging and methodology for efficiently and repeatably creating aerosolized bursts of a peptide hormone drug (e.g., drugs used in endocrine therapy such as leuprolide or calcitonin) containing formulation are disclosed. Devices are hand-held, self-contained units which are automatically actuated at the same release point in a patient's inspiratory flow cycle. The release point is automatically determined either mechanically or, more preferably calculated by a microprocessor which receives data from a sensor making it possible to determine inspiratory flow rate and inspiratory volume. The device is loaded with a cassette comprised of an outer housing which holds a package of individual disposable collapsible containers of a peptide hormone drug containing formulation for systemic delivery. Actuation of the device forces a peptide hormone drug formulation through a porous membrane of the container which membrane has pores having a diameter in the range of about 0.25 to 3.0 microns, preferably 0.25 to 1.5 microns. The porous membrane is positioned in alignment with a surface of a channel through which a patient inhales air. The flow profile of air moving through the channel is such that the flow at the surface of the channel is less than the flow rate at the center of the channel. The membrane is designed so that it protrudes outward at all times or made flexible so that when a peptide hormone drug formulation is forced against and

- 6 -

through the membrane the flexible membrane protrudes outward beyond the flow boundary layer of the channel into faster moving air. Because the membrane protrudes into the faster moving air of the channel the particles of aerosol  
5 formed are less likely to collide allowing for the formation of a burst of fine aerosol mist with uniform particle size.

Smaller particle sizes are preferred to obtain systemic delivery of a peptide hormone drug. Thus, in one  
10 embodiment, after the aerosolized mist is released into the channel energy is actively added to the particles in an amount sufficient to evaporate carrier and thereby reduce particle size. The air drawn into the device is actively heated by moving the air through a heating material which  
15 material is pre-heated prior to the beginning of a patient's inhalation. The amount of energy added can be adjusted depending on factors such as the desired particle size, the amount of the carrier to be evaporated, the water vapor content of the surrounding air and the composition of  
20 the carrier.

To obtain systemic delivery it is desirable to get the aerosolized a peptide hormone drug formulation deeply into the lung. This is obtained per the present invention, in part, by adjusting particle sizes. Particle diameter  
25 size is generally about twice the diameter of the pore from which the particle is extruded. In that it is technically difficult to make pores of 2.0 microns or less in diameter the use of evaporation can reduce particle size to 3.0 microns or less even with pore sizes well above 1.5  
30 microns. Energy may be added in an amount sufficient to evaporate all or substantially all carrier and thereby provide particles of dry powdered a peptide hormone or highly concentrated a peptide hormone drug formulation to a patient which particles are uniform in size regardless of  
35 the surrounding humidity and smaller due to the evaporation



- 7 -

of the carrier. Air drawn into the device by the patient may be drawn through a desiccator containing a desiccant which removes moisture from the air thereby improving evaporation efficiency when the carrier is water.

5 Alternatively, water vapor or aerosolized water may be introduced to the channel to saturate inhaled air thereby preventing evaporation of carrier and maintaining particle size. By adding energy some or all carrier can be evaporated. Alternatively, by adding water evaporation can

10 be prevented. Either procedure provides a desired result in that the size of the particles may be modified or maintained regardless of the surrounding humidity of the air where the device is used.

In addition to adjusting particle size, systemic

15 delivery of a peptide hormone drug is obtained by releasing an aerosolized dose at a desired point. When providing systemic delivery it is important that the delivery be reproducible.

Reproducible dosing is obtained by providing for

20 automatic release at the same inspiratory flow rate and inspiratory volume (determined in real time) each time drug is released. The methodology involves measuring for, determining and/or calculating a firing point or drug release decision based on instantaneously (or real time)

25 calculated, measured and/or determined inspiratory flow rate and inspiratory volume points. The device includes a timer to enable a patient to take a drug at the same time each day. Further, overadministration of hormone formulations is avoided by providing a pre-programmed

30 microprocessor designed to avoid overdosing.

It is an object of this invention to describe a device which aerosolizes peptide hormone drugs held in a dual compartment container with a first compartment holding drug and a second holding liquid.

- 8 -

An advantage of the present invention is that it can be used for ambulatory patients.

It is a feature of the invention that the device used for the aerosolized delivery of hormone formulations  
5 records the time and amount of formulation delivered.

Another advantage of the present invention is that the device used for delivering hormone formulations includes a timer which emits an audible and/or visual signal to the patient at each scheduled dosing event.

10 Yet another advantage of the present invention is that the method involves administering hormone formulations while simultaneously keeping an index which corresponds to the quality of the patient's inspiratory flow profile at each dosing event.

15 Another feature of the present invention is that when carrying out the method of delivery, a record of the date and time of each dosing event is electronically and automatically produced within a unitary device which delivers the drug.

20 Another advantage of the present invention is that the device presents a visual display calendar which calendar specifically indicates to the patient the day and/or time a dose was administered.

Another feature of the present invention is that the  
25 device for administering drug includes a microprocessor programmed to prevent the administration of more doses than are prescribed for the particular deficiency being treated.

Another advantage of the present invention is that better treatment protocols can be developed by the treating  
30 physician by transferring information from the delivery/recording device to a printout device which can be reviewed in order to determine the complete compliance history of the patient.

Another object of this invention is to provide an  
35 apparatus which can analyze the breathing pattern of the

- 9 -

patient and can measure the respiratory flow rate and measure the inspiratory volume at the same time in order to determine the optimal point in the inspiratory cycle for delivery of aerosolized peptide drugs.

5 Another advantage is that the method described provides for reproducible delivery of peptide hormones such as leuprolide wherein the reproducibility is a critical part of treatment causing each dose of hormone to have the same clinical effect.

10 Another object is to provide a method of providing endocrine therapy to ambulatory patients wherein an aerosolized formulation of a peptide drug is repeatedly delivered to the patient at the same inspiratory volume (in the range of 0.15 to 1.5 liters) and the same inspiratory  
15 flow rate (in the range of 0.1 to 2.0 liters per sec).

Another feature of this invention is that formulations of peptide drugs such as leuprolide in a highly volatile propellant provide for a fundamentally tamper-resistant package.

20 It is another object of the invention to provide a metered-dose inhaler canister comprising a formulation of a peptide drug such as leuprolide packaged in a manner such that it will remain stable and active for long storage times.

25 A feature of the invention is that it can monitor the amount of aerosolized peptide drug delivered to a patient and record amounts and times of delivery for review by a treating physician.

An object of the invention is to provide a container  
30 which holds an aerosolizable formulation of a peptide hormone drug which container comprises a porous membrane which protrudes outward in a stationary state or on the application of force forming a convex surface when drug formulation is forced against and through the membrane.

- 10 -

Another object is to provide a method for creating an aerosol of a peptide hormone drug formulation which comprises drawing air over a surface of a porous membrane in a channel and forcing formulation against the membrane  
5 so as to protrude the membrane through a flow boundary layer into faster moving air of the channel.

Another object of the invention is to adjust particle size by adding energy to the particles in an amount sufficient to evaporate carrier and reduce total  
10 particle size.

Another object is to provide a drug delivery device which includes a desiccator for drying air in a manner so as to remove water vapor and thereby provide consistent particle sizes even when the surrounding humidity varies.

15 Another object is to provide a device for the delivery of aerosols which measures humidity via a solid state hygrometer.

A feature of the invention is that drug can be dispersed or dissolved in a liquid carrier such as water  
20 and dispersed to a patient as dry or substantially dry particles.

Another advantage is that the size of the particles delivered will be independent of the surrounding humidity.

These and other objects, advantages and features of  
25 the present invention will become apparent to those skilled in the art upon reading this disclosure in combination with drawings wherein like numerals refer to like components throughout.

#### Brief Description of the Drawings

30 Figure 1 is a cross-sectional view of a container of the invention;

Figure 2 is a cross-sectional view of a preferred embodiment of a container of the invention;

- 11 -

Figure 3 is a cross-sectional view of the container of Figure 2 in use in a channel of a drug delivery device;

Figure 4 is a plan view of a drug delivery device of the invention;

5        Figure 5 is a graph plotting the density of water vapor in air versus temperature;

Figure 6 is a graph plotting the density of ethanol vapor in air versus temperature;

10       Figure 7 is a perspective view of the package of the invention;

Figure 8 is a perspective view of a container of the invention;

15       Figure 9 is a graph showing data points plotted in four general areas with the points plotted relative to inspiratory flow rate (on the abscissa) and inspiratory volume (on the ordinate) in two dimensions;

Figure 10 is a graph showing the four general areas plotted per figure 9 now plotted with a third dimension to show the percentage of drug reaching the lungs based on a  
20       constant amount of drug released;

Figure 11 is a three dimensional graph showing the therapeutic values for inspiratory flow rate and inspiratory volume which provide better drug delivery efficiency;

25       Figure 12 shows a preferred range of the valves shown in figure 11;

Figure 13 shown a particularly preferred range for the valves of figure 11; and

30       Figure 14 is a schematic view of a dual compartment peptide hormone drug containing container.

#### Detailed Description of the Preferred Embodiments

Before the present method of endocrine therapy and devices, containers, packages and formulations used in connection with such are described, it is to be understood

- 12 -

that this invention is not limited to the particular methodology, devices, packages, containers and formulations described, as such methods, devices, packages, containers and formulations may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a formulation" includes mixtures of different formulations, reference to "an aerosolized compound" includes a plurality of such compounds, and reference to "the method of treatment" includes reference to equivalent steps and methods known to those skilled in the art, and so forth.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, the preferred methods and materials are now described. All documents mentioned herein are incorporated herein by reference to describe and disclose specific information for which the document was cited in connection with.

#### Definitions

The terms "hormone," "hormone drug," "pharmaceutically active hormone formulation," "peptide used in endocrine therapy," "peptide hormone drug," "peptide drug" and the like are used interchangeably herein. A hormone drug as described herein is a peptide drug which has been prepared in a pharmaceutically

- 13 -

effective formulation and is useful in endocrine therapy. Specifically, a peptide drug of the type described herein is useful for exogenously modifying the behavior of a patient's endocrine system. Drugs which are used in the present invention include those listed in Table 1, it being noted that these peptides preferably contain less than 50, more preferably less than 27, amino acids. Drug of smaller size are preferred. Particularly useful drugs for use with the invention include leuprolide and calcitonin, and nafarelin. The containers, devices and methods disclosed herein can be used to create an aerosol for inhalation into the lungs using any pharmaceutically active peptide. Examples of useful peptides include:

Interferon-alpha  
15 Interferon-gamma  
HPTH (human parathyroid hormone)  
GCSF (granulocyte colony stimulating factor)  
GMCSF (granulocyte macrophage colony stimulating factor)  
Atrial natriuretic factor  
20 Angiotensin inhibitor  
Renin inhibitor  
Somatomedin  
FSH (follicle stimulating hormone)  
Tissue growth factors (TGF's)  
25 Endothelial growth factors  
HGF (hepatocyte growth factor)  
Amylin  
Factor VIII  
Vasopressin  
30 IIB/IIIA peptide antagonists

The invention is intended to cover such pharmaceutically active peptides, which are synthetic, naturally occurring, glycosylated, unglycosylated, pegylated forms and biologically active analogs thereof.

35 The term "dosing event" shall be interpreted to mean the administration of peptide drug to a patient in need thereof by the intrapulmonary route of administration which event may encompass one or more releases of drug formulation from a drug dispensing device over a period of

- 14 -

time of 15 minutes or less, preferably 10 minutes or less, and more preferably 5 minutes or less, during which period multiple inhalations are made by the patient and multiple doses of peptide drug are released and inhaled. A dosing  
5 event shall involve the administration of peptide drug to the patient in an amount of about 1  $\mu$ g to about 10 mg in a single dosing event which may involve the release of from about 10  $\mu$ g to about 100 mg of peptide drug from the device.

10 The term "velocity of the drug" or "velocity of particles" shall mean the average speed of particles of respiratory drug formulation moving from a release point such as a porous membrane or a valve to a patient's mouth. In a preferred embodiment the velocity of the particles is  
15 zero or substantially zero in the absence of flow created by patient inhalation.

The term "bulk flow rate" shall mean the average velocity at which air moves through a channel considering that the flow rate is at a maximum in the center of the  
20 channel and at a minimum at the inner surface of the channel.

The term "flow boundary layer" shall mean a set of points defining a layer above the inner surface of a channel through which air flows wherein the air flow rate  
25 below the boundary layer is substantially below the bulk flow rate, e.g., 50% or less than the bulk flow rate.

The term "carrier" shall mean a liquid, flowable, pharmaceutically acceptable excipient material which peptide hormone drug is suspended in or more preferably  
30 dissolved in. Useful carriers do not adversely interact with the peptide hormone drug and have properties which allow for the formation of aerosolized particles preferably particles having a diameter in the range of 0.5 to 3.0 microns when a formulation comprising the carrier and  
35 respiratory drug is forced through pores having a diameter



- 15 -

of 0.25 to 3.0 microns. Preferred carriers include water, ethanol and mixtures thereof. Other carriers can be used provided that they can be formulated to create a suitable aerosol and do not adversely effect the peptide hormone drug  
5 on human lung tissue.

The term "measuring" describes an event whereby either the inspiratory flow rate or inspiratory volume of the patient is measured in order to determine an optimal point in the inspiratory cycle at which to release  
10 aerosolized drug. An actual measurement of both rate and volume may be made or the rate can be directly measured and the volume calculated based on the measured rate. It is also preferable to continue measuring inspiratory flow during and after any drug delivery and to record  
15 inspiratory flow rate and volume before, during and after the release of drug. Such reading makes it possible to determine if drug was properly delivered to the patient.

The term "measuring" describes an event whereby both the inspiratory flow rate and inspiratory volume of the  
20 patient is determined, measured and/or calculated in order to determine an optimal point in the inspiratory cycle at which to release aerosolized peptide drug formulation. It is also preferable to continue measuring inspiratory flow during and after any drug delivery and to record  
25 inspiratory flow rate and volume before, during and after the release of drug. Such reading makes it possible to determine if peptide drug formulation was properly delivered to the patient. A microprocessor or other device can calculate volume based on a measured flow rate. When  
30 either flow rate or volume becomes known in any manner it can be said to have been determined.

The term "monitoring" event shall mean measuring lung functions such as inspiratory flow rate, and/or inspiratory volume so that a patient's lung function as  
35 defined herein, can be evaluated before and/or after drug

- 16 -

delivery thereby making it possible to evaluate the effect, if any, of peptide drug delivery on the patient's lung function.

The term "inspiratory flow rate" shall mean a value  
5 of air flow measured, calculated and/or determined based on the speed of the air passing a given point in a measuring device assuming atmospheric pressure  $\pm 5\%$  and a temperature in the range of about  $10^{\circ}\text{C}$  to  $40^{\circ}\text{C}$ .

The term "inspiratory flow" shall be interpreted to  
10 mean a value of air flow calculated based on the speed of the air passing a given point along with the volume of the air that has passed that point with the volume calculation being based on integration of the flow rate data and assuming atmospheric pressure,  $\pm 5\%$  and temperature in the  
15 range of about  $10^{\circ}\text{C}$  to about  $40^{\circ}\text{C}$ .

The term "inspiratory volume" shall mean a measured, calculated and/or determined volume of air passing a given point into the lungs of a patient assuming atmospheric pressure  $\pm 5\%$  and a temperature in the range of  $10^{\circ}\text{C}$  to  
20  $40^{\circ}\text{C}$ .

The term "inspiratory flow profile" shall be interpreted to mean data calculated in one or more events measuring inspiratory flow and cumulative volume, which profile can be used to determine a point within a patient's  
25 inspiratory cycle which is optimal for the release of drug to be delivered to a patient. The point within the inspiratory cycle where drug is released may be based on a point within the inspiratory cycle likely to result in the maximum delivery of drug and based and/or on a point in the  
30 cycle most likely to result in the delivery of a reproducible amount of drug to the patient at each release of drug. Repeatability of the amount delivered is the primary criterion and maximizing the amount delivered is an important but secondary criterion. Thus, a large number of  
35 different drug release points might be selected and provide



- 18 -

function most commonly employed in clinical practice involve timed measurement of inspiratory and expiratory maneuvers to measure specific parameters. For example, forced vital capacity (FVC) measures the total volume in  
5 liters exhaled by a patient forcefully from a deep initial inspiration. This parameter, when evaluated in conjunction with the forced expired volume in one second ( $FEV_1$ ), allows bronchoconstriction to be quantitatively evaluated. A problem with forced vital capacity determination is that  
10 the forced vital capacity maneuver (i.e. forced exhalation from maximum inspiration to maximum expiration) is largely technique dependent. In other words, a given patient may produce different FVC values during a sequence of consecutive FVC maneuvers. The FEF 25-75 or forced  
15 expiratory flow determined over the mid-portion of a forced exhalation maneuver tends to be less technique dependent than the FVC. Similarly, the  $FEV_1$  tends to be less technique dependent than FVC. In addition to measuring volumes of exhaled air as indices of pulmonary function,  
20 the flow in liters per minute measured over differing portions of the expiratory cycle can be useful in determining the status of a patient's pulmonary function. In particular, the peak expiratory flow, taken as the highest air flow rate in liters per minute during a forced  
25 maximal exhalation, is well correlated with overall pulmonary function in a patient with asthma and other respiratory diseases. The present invention carries out treatment by administering drug in a drug delivery event and monitoring lung function in a monitoring event. A  
30 series of such events may be carried out and repeated over time to determine if lung function is improved.

Each of the parameters discussed above is measured during quantitative spirometry. A patient's individual performance can be compared against his personal best data,  
35 individual indices can be compared with each other for an

- 19 -

individual patient (e.g. FEV<sub>1</sub> divided by FVC, producing a dimensionless index useful in assessing the severity of acute asthma symptoms), or each of these indices can be compared against an expected value. Expected values for  
5 indices derived from quantitative spirometry are calculated as a function of the patient's sex, height, weight and age. For instance, standards exist for the calculation of expected indices and these are frequently reported along with the actual parameters derived for an individual  
10 patient during a monitoring event such as a quantitative spirometry test.

The term "substantially dry" shall mean that particles of formulation including an amount of carrier (e.g. water or ethanol) which is equal to (in weight) or  
15 less than the amount of drug in the particle. Preferable such particles consist essentially of only analgesic drug with no free carrier e.g., no free water.

The terms "aerosolized particles" and "aerosolized particles of formulation" shall mean particles of  
20 formulation comprised of pharmaceutically active peptide hormone drug and carrier which are formed upon forcing the formulation through a nozzle which nozzle is preferably in the form of a flexible porous membrane. The particles have a size which is sufficiently small such that when the  
25 particles are formed they remain suspended in the air for a sufficient amount of time such that the patient can inhale the particles into the patient's lungs. Preferably, the particles have a size in the range of 0.5 micron to about 12 microns having been created by being forced  
30 through the pores of a flexible porous membrane which pores have a diameter in the range of about 0.25 micron to about 6.0 microns -- the pores being present on the membrane in an amount of about ten to 10,000 pores over an area in size of from about 1 sq. millimeter to about 1 sq. centimeter.

- 20 -

General Methodology

Devices, containers and methods are disclosed which provide a non-invasive means of endocrine therapy which makes it possible to maintain tight control over the amount of drug administered to a patient and precise timing in terms of when the drug is administered. The invention provides aerosolized delivery of a peptide drug to the patient in a controlled and repeatable manner. The device of the invention provides a number of features which make it possible to achieve the controlled and repeatable dosing procedure required for successful endocrine therapy. Specifically, the device is not directly actuated by the patient in the sense that no button is pushed nor valve released by the patient applying physical pressure. On the contrary, the device of the invention releases peptide hormone drug automatically upon receipt of a signal from a microprocessor programmed to send a signal when data is received from a monitoring device such as an airflow rate monitoring device.

Delivery devices used to carry out the present invention record specific information relating to both monitoring events and dosing events and can be programmed to react to various changes in order to optimize patient treatment. Specifically, the device includes an ability to record monitoring events in order to develop an inspiratory flow profile of the patient which makes it possible to provide for greater repeatability with respect to dosing. Further, the device specifically records the time and amount of hormone drug released at each dosing event. The day and time of day of drug release is recorded. The device is equipped with a visual and audio signaling means which tell the patient when and/or how much peptide drug to take. The audio means is programmed so as to send an audio signal when the patient is to begin a monitoring event to be followed by a dosing event. The visual display

- 21 -

indicates specific information such as providing instructions to the patient including "conduct monitoring event" and "proceed with dosing event." Further, the visual display will indicate a calendar of days and  
5 specifically indicate on the calendar when dosing took place on the given day. Accordingly, the patient can quickly determine by visual examination whether peptide hormone drug was delivered on any given day. It is important to administer peptide hormone drugs at the same  
10 time each day as natural hormone release (and thus hormone administration) is closely connected to the chronobiology of the patient.

A patient using the device withdraws air from a mouthpiece and the inspiratory rate, and calculated  
15 inspiratory volume of the patient are measured one or more times in a monitoring event which determines a preferred point in an inhalation cycle for the release of a dose of peptide drug. Inspiratory flow is measured and recorded in one or more monitoring events for a given patient in order  
20 to develop an inspiratory flow profile for the patient. The recorded information is analyzed by the microprocessor in order to deduce a preferred point within the patient's inspiratory cycle for the release of peptide drug with the preferred point being calculated based on the most likely  
25 point to result in a reproducible delivery event.

It is pointed out that the device of the present invention can be used to, and actually does, improve the efficiency of drug delivery. However, this is a secondary feature. The primary feature is the reproducibility of the  
30 release of a tightly controlled amount of drug at a particular point in the respiratory cycle so as to assure the delivery of a controlled and repeatable amount of drug to the lungs of each individual patient.

The combination of automatic control of the valve  
35 release, combined with frequent monitoring events in order

- 22 -

to calculate the optimal flow rate and time for the release of peptide drug, combine to provide a repeatable means of delivering peptide drug to a patient. Because aerosolized peptide hormone drug is released automatically and not manually, it can be predictably and repeatedly be released in the same amount each time to provide a preprogrammed measured amount which is desired. Because dosing events are preferably preceded by monitoring events, the amount of peptide drug released and/or the point in the inspiratory cycle of the release can be readjusted based on the particular condition of the patient. For example, if the patient is suffering from a condition which allows for a certain degree of pulmonary insufficiency, such will be taken into account in the monitoring event by the microprocessor which will readjust the amount and/or point of release of the peptide drug in a manner calculated to provide for the administration of the same amount of peptide hormone drug to the patient at each dosing event. To obtain controlled repeatable dosing a number of factors are preferably considered. Specifically, one should adjust:

(1) the release point within a patient's inspiratory flow rate inside a range of about 0.10 to about 2.0 liters/second preferably about 0.2 to about 1.8 liters per sec. and more preferably 0.15 to 1.7 liters per sec;

(2) the release point within a patient's inspiratory volume of about 0.15 to about 2.0 liters preferably 0.15 to 0.8 liters and more preferably 0.15 to about 0.4 liters;

(3) particle size for systemic delivery in a range of about 0.5 to 6 microns and more preferably 0.5 to about 3 microns;

(4) the concentration of the drug in the carrier in the range of from about 0.01% to about 12.5% ;



- 23 -

(5) the amount of heat added to the air about 20 Joules to about 100 Joules and preferably 20 Joules to about 50 Joules per 10  $\mu$ l of formulation;

(6) the relative volume of air added by patient inhalation per 10  $\mu$ l of formulation at about 100 ml to 2 l and preferably about 200 ml to 1 liter for evaporation and without evaporation 50-750 ml preferably 200-400 ml;

(7) the rate of vibration of the porous membrane from 575 to 17,000 kilohertz;

(8) pore size to a range of about 0.25 to about 6.0 microns in diameter preferably 0.5 to 3 microns and more preferably 1-2 microns;

(9) viscosity of the formulation to a range of from about 25% to 1,000% of the viscosity of water;

(10) extrusion pressure in a range of about 50 to 600 psi and preferably 100 to 500 psi;

(11) ambient temperature to 15°C to 30°C and ambient pressure between 1 atmosphere and 75% of 1 atmosphere;

(12) the ratio of liquid carriers to each other to be consistent;

(13) the solubility of drug to carrier to obtain a high concentration of a peptide hormone in the carrier;

(14) the desiccator to maximize removal of water vapor from air;

(15) the shape of the pore opening to be circular in diameter and a conical in cross-section with the ratio of the diameter of the small to large end of the cone being about  $\frac{1}{2}$  to  $\frac{1}{20}$ , and the shape of the porous membrane to an elongated oval;

(16) the thickness of the membrane to 5 to 200 microns; preferably 10 - 50 microns;

(17) the membrane to have a convex shape or to be flexible so that it protrudes outward in a convex shape beyond the flow boundary layer when formulation is forced through it. and

- 24 -

(18) the firing point to be at substantially the same point at each release for the parameters (1-17), i.e., each release of drug is at substantially the same point so as to obtain repeatability of dosing.

## 5 Flow/Volume Parameters

Figure 9 is a two-dimensional graph wherein the inspiratory flow rate is plotted against the inspiratory volume. The patient's inspiratory flow rate and inspiratory volume are simultaneously and separately measured. The measurement is taken and the information obtained from the measurement provided to a microprocessor which microprocessor is programmed to release drug (1) at the same point relative to inspiratory flow and inspiratory volume at each release of drug and (2) to select that point within prescribed parameters of inspiratory flow rates and inspiratory volumes. In the particular results plotted in figure 9 the microprocessor was programmed to release drug in four general areas with respect to the inspiratory flow rate and inspiratory volume parameters. This resulted in data points being plotted in four general areas on the two-dimensional graph of figure 9. The four areas are labeled A, B, C and D. In area A (showing solid triangles), the drug was released when the patient's inspiratory flow rate was "slow to medium" (0.10 to 2.0 liters per sec) with an "early" inspiratory volume of 0.15 to 0.8 liters. In area B (showing open triangles), the drug was released at a "slow" inspiratory rate (0.10 to 1.0 liters/sec) and a "late" volume (1.6 to 2.8 liters). In area C (showing solid diamonds), the drug was released at a "fast" inspiratory flow rate (3.5 to 4.5 liters/sec) and a "late" volume. In area D (showing solid circles), the drug was released at a "fast" inspiratory flow rate and an "early" inspiratory volume.

- 25 -

The results shown in figure 9 were obtained while administering a radioactively labeled drug to a human. After the administration of the drug it was possible to determine not only the amount of drug, but the pattern of drug deposited within the lungs of the patient. Using this information two conclusions were reached. Firstly, it was determined that it is important to simultaneously and separately consider (in real time) both inspiratory flow rate and inspiratory volume when determining the point for drug release for intrapulmonary drug delivery. Changes in either parameter can greatly effect the amount of drug deposited. Thus, when treating a patient the drug should be released at approximately ( $\pm 10\%$ , preferably  $\pm 5\%$  and most preferable as close as possible to the first release point) the same inspiratory flow rate and inspiratory volume each time - going back to the same point each time for the same patient ensures repeatable dosing. In practice the tighter the point is defined the greater the repeatability of dosing. However, if the point is defined to precisely it can be difficult for the patient to obtain that rate/volume point again. Thus, some degree of tolerance is generally applied. Secondly, it was found that within particular ranges with respect to inspiratory flow rate and inspiratory volume it was possible to obtain a consistently high percentage amount of drug deposited in the lung. Such results are shown graphically within the three dimensional graph as shown in figure 10.

The third dimension as shown in figure 10 (the height of the four columns) indicates the percentage amount of drug deposited based on the total amount of drug released to the patient. The area labeled A clearly showed the highest percentage of drug delivered to the patient based on the amount of drug released. Using this information it was possible to calculate a specific area regarding inspiratory flow rate and inspiratory volume at

- 26 -

which it is possible to obtain not only a high degree of repeatability in dosing, but obtain a higher percentage of drug being delivered based on the percentage of drug released. Specifically, it was determined that the drug  
5 should be released within an inspiratory flow rate range of 0.10 to 2.0 liters per second and at an inspiratory volume in the range of about 0.15 to about 0.80 liters. This range is shown by the rectangularly shaped column of figure 11.

10 In that intrapulmonary drug delivery systems often provide for erratic dosing it is important to provide a method which allows for consistent, repeatable dosing. This is obtained by simultaneously and separately considering both inspiratory flow rate and inspiratory  
15 volume in order to determine a point by its abscissa and ordinate. If both measurements are separately considered the drug can be released anywhere along the abscissa and ordinate scales shown in figure 9. Once a point is selected (such as by randomly selecting a point in box A of  
20 the graph of figure 9) that selected point (with the same coordinants) is used again and again by a given patient to obtain repeatable dosing. If only one parameter is measured (abscissa or ordinate) and drug is released based on that parameter the drug release point is defined by a  
25 line on the graph of figure 5. When drug is released again the release can be at any point on that line. For example, the inspiratory flow rate (measured horizontally on the abscissa) might be defined by a point. However, the inspiratory volume (which was not measured and/or  
30 considered) would be defined only by a vertical line. Thus, subsequent releases would be at different volumes along that vertical line and the dosing would not be consistent. By measuring both inspiratory flow rate on the abscissa and inspiratory volume on the ordinant the  
35 coordinants will mark a point for drug release. That point

- 27 -

can be found again and again to obtain repeatability in dosing. The same point should be selected each time as closely as possible and within a margin of errors of  $\pm 10\%$  with respect to each criteria. The margin for error can be  
5 increased and still maintain acceptable levels of repeatable dosing - but the error should keep the drug release point inside the box A of figure 9.

By examining delivery of drug associated with the data points plotted in figure 9, it is possible to  
10 determine a preferred and particularly preferred and most preferred range as per figures 11, 12 and 13. The preferred range of figure 11 shows drug released at a volume of 0.15 to 0.8 liters and rate of 0.10 to 2.0 liters/second. The particularly preferred range plotted in  
15 figure 12 indicates that the inspiratory flow should be within the range of 0.2 to about 1.8 liters per second with an inspiratory volume in the range of 0.15 to about 0.4 liters. The most preferred range (figure 13) is from about 0.15 to about 1.8 liters per second for the inspiratory  
20 flow rate and about 0.15 to about 0.25 liters for the inspiratory volume. Thus, preferred delivery can be obtained by (1) repeatedly delivering aerosolized formulation to a patient at the same simultaneously and separately measured inspiratory flow rate and inspiratory  
25 volume and (2) releasing drug to the patient within specified therapeutically effective ranges as shown within figures 11, 12 and 13. The invention involves releasing drug (after measuring) inside the ranges as per figures 11, 12 or 13. Thus, the release could begin inside or outside  
30 the range. Preferably the drug release begins inside the range and more preferable begins and ends inside the ranges of figures 11, 12 or 13.

The methodology of the invention may be carried out using a portable, hand-held, battery-powered device as  
35 described using a microprocessor as disclosed in U.S.

- 28 -

Patents Nos. 5,404,871, issued April 11, 1995 and 5,450,336, issued September 12, 1995 incorporated herein by reference. In accordance with the system the drug is included in an aqueous formulation which is aerosolized by moving the formulation through a flexible porous membrane which obtains a convex configuration in use or has a convex permanent configuration. Alternatively, the methodology of the invention could be carried out using a mechanical (non-electronic) device. Those skilled in the art recognized that various components can be mechanically set to actuate at a given inspiratory flow rate (e.g. a spring biased valve) and at a given volume (e.g. a spinable flywheel which rotates a given amount per a given volume). The components of such devices could be set to allow drug release inside the parameters of figures 11, 12 or 13.

The drug which is released to the patient may be in a variety of different forms. For example, the drug may be an aqueous solution of drug, i.e., drug dissolved in water and formed into small particles to create an aerosol which is delivered to the patient. Alternatively, the drug may be in a solution wherein a low-boiling point propellant is used as a solvent.

Some peptide drugs are subject to being degraded more quickly when in solution such as an aqueous solution. Preferably such drug are packaged in a dry form and mixed with water prior to administration. A dual compartment container for carrying out such is shown in figure 14. Alternately, the drug is kept in the form of a dry powder which is intermixed with an airflow in order to provide for particlized delivery of drug to the patient.

Regardless of the type of drug or the form of the drug formulation, it is preferable to create drug particles having a size in the range of about 0.5 to 5 microns. By creating drug particles which have a relatively narrow range of size, it is possible to further increase the

- 29 -

efficiency of the drug delivery system and improve the repeatability of the dosing. Thus, it is preferable that the particles not only have a size in the range of 0.5 to 5 microns but that the mean particle size be within a narrow range so that 80% or more of the particles being delivered to a patient have a particle diameter which is within  $\pm 50\%$  of the average particle size, preferably  $\pm 20\%$  and more preferably  $\pm 5\%$  of the average particle size.

The velocity at which the aerosolized drug is released to the patient is also important in terms of obtaining a high degree of repeatability in dosing and providing for a high percentage of drug being delivered to the patient's lungs. Most preferably, the drug is released from a container in a direction which is normal to the patient's airflow. Accordingly, the drug may be released directly upward so that its flow is at a  $90^\circ$  angle with respect to the patient's inspiratory flow which is directly horizontal. After being released, the drug velocity decreases and the drug particles remain suspended for a sufficient period of time to allow the patient's inspiration to draw the drug into the patient's lungs. The velocity of drug released in the direction from the drug release point to the patient may match the patient's inspiratory flow rate but is preferably slower than the patient's inspiratory flow rate and is most preferably about zero in the absence of inspiratory flow. The velocity may be slightly negative, i.e., in a direction away from the patient. The velocity may range from -2.0 liters/sec to 2.0 liters/sec and is preferably zero in the absence of patient inhalation. It is not desirable to project the drug toward the patient at a rate above the speed of the patient's breath as such may result in drug being deposited on the back of the patient's throat. Thus, the drug release speed should be equal to or less than the breath speed. The actual speed of release can vary

- 30 -

depending on factors such as the particle size, the particle composition and the distance between the point of release and the patient. The velocity is preferably such that the particles will (due to air resistance) slow to  
5 zero velocity (in the absence of patient inhalation) after traveling a distance of about 2 centimeters or less. In general, the shorter the distance required to slow the particles to zero velocity the better.

An aerosol may be created by forcing drug through  
10 pores of a membrane which pores have a size in the range of about 0.5 to 6.0 microns but preferably 0.25 to 2.5 microns to obtain better systemic delivery. When the pores have this size the particles which escape through the pores to create the aerosol will have a diameter in the range of  
15 about 0.5 to 5 microns i.e., about twice the size of the pores. Drug particles may be released with an air flow intended to keep the particles within this size range. Heating the air prior to contact with the particles is useful in that it promotes evaporation and reduces particle  
20 size.

The creation of small particles may be facilitated by the use of the vibration device which provides a vibration frequency in the range of about 575 to about 32,000 kilohertz. Those skilled in the art will recognize  
25 that some adjustments can be made in the parameters such as the size of the pores from which drug is released, vibration frequency, pressure, and other parameters based on the density and viscosity of the formulation keeping in mind that the object is to provide aerosolized particles  
30 having a diameter in the range of about 0.5 to 5 microns.

The drug formulation may be a low viscosity liquid formulation. The viscosity of the drug by itself or in combination with a carrier is not of particular importance except to note that the formulation must have  
35 characteristics such that it can be forced out of openings



- 31 -

to form an aerosol, e.g., using pressure (e.g., 20 to 500 psi) to form an aerosol preferably having a particle size in the range of about 0.5 to 5 microns.

Drug may be stored in and/or released from a container of any desired size. In most cases the size of the container is not directly related to the amount of drug being delivered in that most formulations include relatively large amounts of excipient material e.g. water or a saline solution. Accordingly, a given size container could include a wide range of different doses by varying drug concentration.

The amount of peptide drug delivered to the patient will vary greatly depending on the particular drug being delivered. In accordance with the present invention it is possible to deliver a wide range of peptide drugs. For example, drugs included within the container could be drugs which have a systemic effect e.g. leuprolide or a local effect in the lungs e.g. Activase.

Drug containers may include indices which may be electronic and may be connected to a power source such as a battery. When the indices are in the form of visually perceivable numbers, letters or any type of symbol capable of conveying information to the patient. Alternatively, the indices may be connected to a power source such as a battery when the indices are in the form of magnetically, optically or electronically recorded information which can be read by a drug dispensing device which in turn provides visual or audio information to the user. The indices can be designed for any desired purpose but in general provides specific information relating to the day and/or time which the drug within a container should be administered to the patient. Such indices may record, store and transfer information to a drug dispensing device regarding the number of doses remaining in the container. The containers may include labeling which can be in any format and could

- 32 -

include days of the month or other symbols or numbers in any variation or language.

In addition to disclosing specific information regarding the day and time for drug delivery the indices  
5 could provide more detailed information such as the amount of drug dispensed from each container which might be particularly useful if the containers included different amounts of drug. Further, magnetic, optical and/or electronic indices could have new information recorded onto  
10 them which information could be placed there by the drug dispensing device. For example, a magnetic recording means could receive information from the drug dispensing device indicating the precise time which the drug was actually administered to the patient. In addition to recording the  
15 time of delivery the device could monitor the expected efficacy of the delivery based on factors such as the inspiratory flow rate which occurred following the initial release of drug. The information recorded could then be read by a separate device, interpreted by the care-giver  
20 and used to determine the usefulness of the present treatment methodology. For example, if the patient did not appear to be responding well but the recorded information indicating that the patient had taken the drug at the wrong time or that the patient had misdelivered drug by changing  
25 inspiratory flow rate after initial release it might be determined that further education in patient use of the device was needed but that the present dosing methodology might well be useful. However, if the recordings indicated that the patient had delivered the drug using the proper  
30 techniques and still not obtained the correct results a different drug or dosing methodology might be recommended.

The method of endocrine therapy may be carried out using a hand-held, portable device comprised of (a) a device for holding a disposable package comprised of at  
35 least one but preferably a number of drug containers, (b) a

- 33 -

propellant or a mechanical mechanism for moving the contents of a container through a porous membrane (c) a monitor for analyzing the inspiratory flow, rate and volume of a patient, and (d) a switch for automatically releasing  
5 or firing the mechanical means after the inspiratory flow and/or volume reaches a threshold level. The device may also include a transport mechanism to move the package from one container to the next with each container and its porous membrane being disposed of after use. The entire  
10 device is self-contained, light weight (less than 1 kg preferably less than 0.5 kg loaded) and portable.

The device may include a mouth piece at the end of the flow path, and the patient inhales from the mouth piece which causes an inspiratory flow to be measured within the  
15 flow path which path may be in a non-linear flow-pressure relationship. This inspiratory flow causes an air flow transducer to generate a signal. This signal is conveyed to a microprocessor which is able to convert, continuously, the signal from the transducer in the inspiratory flow path  
20 to a flow rate in liters per minute. The microprocessor can further integrate this continuous air flow rate signal into a representation of cumulative inspiratory volume. At an appropriate point in the inspiratory cycle, the microprocessor can send a signal to an actuation means  
25 (and/or a vibration device below the resonance cavity). When the actuation means is signaled, it causes the mechanical means (by pressure or vibration) to move drug from a container on the package into the inspiratory flow path of the device and ultimately into the patient's lungs.  
30 After being released, the drug and carrier will pass through a porous membrane which is vibrated to aerosolize the formulation and thereafter the lungs of the patient.

It is important to note that the firing threshold of the device is not based on a single criterion such as the  
35 rate of air flow through the device or a specific time

- 34 -

after the patient begins inhalation. The firing threshold is based on an analysis of the patient's inspiratory flow profile and picking a firing point inside a box as per figures 9-13. This means that the microprocessor  
5 controlling the device takes into consideration the instantaneous air flow rate as well as the cumulative inspiratory flow volume. Both are simultaneously considered together in order to determine the optimal point in the patient's inspiratory cycle most preferable in terms  
10 of (1) reproducibly delivering the same amount of drug to the patient with each release of drug by releasing drug at the same point each time and maximizing the amount of drug delivered as a percentage of the total amount of drug released by releasing with the parameters described herein.

15 The device preferably includes a means for recording a characterization of the inspiratory flow profile for the patient which is possible by including a microprocessor in combination with a read/write memory means and a flow measurement transducer. By using such devices, it is  
20 possible to change the firing threshold at any time in response to an analysis of the patient's inspiratory flow profile, and it is also possible to record drug dosing events over time. In a particularly preferred embodiment the characterization of the inspiratory flow can be  
25 recorded onto a recording means on the disposable package.

The details of a drug delivery device which includes a microprocessor and pressure transducer of the type which may be used in connection with the present invention are described and disclosed within U.S. Patents Nos. 5,404,871,  
30 issued April 11, 1995 and 5,450,336, issued September 12, 1995 by reference, and it is specifically incorporated in order to describe and disclose the microprocessor and program technology used therewith.

The pre-programmed information is contained within  
35 a nonvolatile memory which can be modified via an external

- 35 -

device. In another embodiment, this pre-programmed information is contained within a "read only" memory which can be unplugged from the device and replaced with another memory unit containing different programming information.

5 In yet another embodiment, a microprocessor, containing read only memory which in turn contains the pre-programmed information, is plugged into the device. For each of these embodiments, changing the programming of the memory device readable by a microprocessor will radically change the

10 behavior of the device by causing the microprocessor to be programmed in a different manner. This is done to accommodate different drugs for different types of treatment.

In a preferred embodiment of the methodology of the

15 invention several different criteria are considered.

(1) The inspiratory flow rate and inspiratory volume are simultaneously and separately considered to insure repeatability. (2) The drug is released inside the parameters of figures 11, 12 or 13 with figure 13

20 parameters being most preferred. (3) The particle size of the released drug is in the range of 0.5 to 5 microns and 80% or more and the particles have the same size as the average particle size  $\pm 10\%$  in size. (4) The drug particles are released at a velocity which is obtained at

25 a flow rate in the range of greater than -2.0 liters/sec. and less than 2.0 liters/sec. As indicated early the actual velocity can vary based on a number of factors. The release velocity should be determined so that the particles are at or are slowed to zero velocity (relative to patient

30 inhalation) after traveling about 0.5 to 2 cm from the release point. The speed being measured from the drug release point in a direction toward the back of the throat of the patient.

After dosing a patient with a systemic peptide drug

35 it is desirable to take blood samples and make adjustments

- 36 -

as needed to obtain the desired drug to blood ratio. In accordance with all methods the patient does not push a button to release drug. The drug is released automatically by signals from the microprocessor using measurements  
5 obtained.

The amount of peptide hormone drug delivered to the patient will vary greatly depending on the particular drug being delivered. In accordance with the present invention it is possible to deliver a wide range of different peptide  
10 hormone drugs. The drugs must pass through pulmonary membranes and, as such, are preferably small—less than 50 amino acids, more preferably, less than 27 amino acids, in size. The most preferred drugs include leuprolide and calcitonin. Peptide hormone drugs are generally  
15 administered to a patient in an amount in the range of about 10  $\mu$ g - 100  $\mu$ g. Useful hormones are listed below in Table 1.

TABLE 1Useful Peptide Hormone Drugs

20	Compound	Amino acids
	Somatostatin	6
	Oxytocin	9
	Desmopressin	9
25	LHRH	10
	Nafarelin	10
	Leuprolide	11
	ACTH analog	17
	Secretin	27
30	Glucagon	29
	Calcitonin	32
	GHRH	40
	Growth hormone	191

The doses administered are based on an assumption  
35 that when intrapulmonary delivery methodology is used the efficiency of the delivery is at a known percent amount,

- 37 -

e.g., approximately 20% to 50% or more and adjustments in the amount released in order to take into account the efficiency of the device. The differential between the amount of hormone drug actually released from the device and the amount of hormone drug actually delivered to the patient varies due to a number of factors. As shown in figures 11-13 devices may be approximately 20% efficient, however, the efficiency can be as low as 10% and as high as 50% or more meaning that as little as 10% of the released peptide hormone drug may actually reach the circulatory system of the patient and as much as 50% or more might be delivered. The efficiency of the delivery will vary somewhat from patient to patient and must be taken into account when programming the device for the release of peptide hormone drug. In general, a conventional metered dose inhaling device is about 10% efficient.

When administering hormone drug using an inhalation device of the present invention, the entire dosing event can involve the administration of anywhere from 1  $\mu$ l to 100 ml, but more preferably involves the administration of approximately 10  $\mu$ l to 10 ml of a formulation containing peptide drug. The large variation in the amounts which might be delivered are due to the fact that different drugs have greatly different potencies and may be present in different concentrations and delivered from devices which vary greatly in terms of the efficiency of drug delivered. The entire dosing event may involve several inhalations by the patient with each of the inhalations being provided with one or multiple bursts of peptide hormone drug from the device.

In addition to drug potency and delivery efficiency, peptide hormone drug sensitivity must be taken into consideration. The present invention makes it possible to vary dosing over time if the sensitivity of the patient

- 38 -

changes and/or if user compliance and/or lung efficiency changes over time.

#### Dosing Methodology

Based on the above, it will be understood that the dosing or amount of drug actually released from the device can be changed based on the most immediately prior monitoring event wherein the inspiratory flow of a patient's inhalation is measured.

The dosing program can be designed with some flexibility. For example, if the patient normally requires 25 mg per day of drug, the microprocessor of the inhalation device can be programmed to prevent further release of the valve after 35 mg have been administered within a given day. Setting a slightly higher limit would allow for the patient to administer additional hormone drug, if needed, due to misdelivery of hormone drug such as due to coughing or sneezing during an attempted delivery.

The ability to prevent overdosing is a characteristic of the device due to the ability of the device to monitor the amount of peptide hormone drug released and calculate the approximate amount of peptide hormone drug delivered to the patient based on monitoring given events. The ability of the present device to prevent overdosing is not merely a monitoring system which prevents further manual actuation of a button. As indicated above, the device used in connection with the present invention is not manually actuated, but is fired (i.e., drug released) in response to an electrical signal received from a microprocessor (which received data from a monitoring device such as a device which monitors inspiratory flow) and allows the actuation of the device upon achieving an optimal point in a inspiratory cycle. When using the present invention, each release of the valve is a release which will administer drug to the patient in that the valve



- 39 -

is released in response to patient inhalation. More specifically, the device does not allow for the release of peptide hormone drug merely by the manual actuation of a button to fire a burst of hormone drug into the air or a container.

The microprocessor will also include a timing device. The timing device can be electrically connected with visual display signals as well as audio alarm signals. Using the timing device, the microprocessor can be programmed so as to allow for a visual or audio signal to be sent when the patient would be normally expected to administer peptide drug. In addition to indicating the time of administration (preferably by audio signal), the device can indicate the amount of peptide drug which should be administered by providing a visual display. For example, the audio alarm could sound alerting the patient that hormone drug should be administered. At the same time, the visual display could indicate "50  $\mu$ g" as the amount of peptide drug to be administered. At this point, a monitoring event could take place. After completion of the monitoring event, administration would proceed and the visual display would continually indicate the remaining amount of peptide drug which should be administered. After the predetermined dose of 50  $\mu$ g had been administered, the visual display would indicate that the dosing event had ended. If the patient did not complete the dosing event by administering the stated amount of peptide drug, the patient would be reminded of such by the initiation of another audio signal, followed by a visual display instructing the patient to continue administration.

Additional information regarding dosing with peptide drug via injection can be found within Wearley, L.L., "Recent Progress in Protein and Peptide Delivery by Noninvasive Router," Critical Reviews in Therapeutic Drug Carrier Systems, 8(4):331-394 (1991) and Harrison's -

- 40 -

Principles of Internal Medicine (most recent edition) published by McGraw Hill Book Company, New York, incorporated herein by reference to disclose information regarding the dosing of hormone drugs.

5 Drug Delivery with Disposable Container

Figure 1 is a cross-sectional view of a container 1 of the invention which is shaped by a collapsible wall 2. The container 1 has an opening covered by a flexible porous membrane 3 which is covered by a  
10 removable layer 4. The membrane 3 may be rigid and protrude upward in a convex configuration away from the formulation 5. When the layer 4 is removed the wall 2 can be collapsed thereby forcing the peptide hormone formulation 5 against the flexible porous membrane 3 which  
15 will then protrude outward in a convex shape.

Figure 2 is a cross-sectional view of a more preferred embodiment of a container 1 of the invention. The container is shaped by a collapsible wall 2. The container 1 includes an opening which leads to an open  
20 channel 6 which channel 6 includes an abutment 7 which is broken upon the application of force created by formulation 5 being forced from the container. When the abutment 7 is broken the formulation 5 flows to an area adjacent to the flexible porous membrane 3 and is prevented from flowing  
25 further in the channel 6 by a non-breakable abutment 8.

Figure 3 is a cross-sectional view of the container 1 of Figure 2 in use. The wall 2 is being crushed by a mechanical component such as the piston 9 shown in Figure 3. The piston may be driven by a spring, compressed gas,  
30 or a motor connected to gears which translate the electric motor's circle motion to linear motion. The formulation 5 is forced into the open channel 6 (breaking the abutment 7 shown in Figure 2) and against and through the membrane 3

- 41 -

causing the membrane 3 to protrude outward into a convex configuration as shown in Figure 3.

The piston 9 has been forced against the container wall 2 after a patient 10 begins inhalation in the direction of the arrow "I". The patient 10 inhales through the mouth from a tubular channel 11. The velocity of the air moving through the flow path 29 of the channel 11 can be measured across the diameter of the channel to determine a flow profile 12, i.e., the air flowing through the channel 11 has a higher velocity further away from the inner surface of the channel. The air velocity right next to the inner surface of the channel 11 (i.e., infinitely close to the surface) is very slow (i.e., approaches zero). A flow boundary layer 13 defines a set of points below which (in a direction from the channel center toward the inner surface of the channel) the flow of air is substantially below the bulk flow rate i.e., 50% or less than the bulk flow rate.

To allow air to flow freely through the channel 11 the upper surface of the flexible porous membrane 3 is substantially flush with (i.e., in substantially the same plane as) the inner surface of the channel 11. Thus, if the membrane 3 remained in place when the formulation 5 move through the pores the formulation would be released into the slow moving or substantially "dead air" below the boundary layer 13. However, the membrane 3 protrudes outward through the boundary layer 13 into the faster moving air. This is desirable in that it aids in avoiding the agglomulation of particles. More specifically, when formulation exits the pores the formulation naturally forms spherical particles. Those particles slow down due to the frictional resistance created by the air through which the particles must travel. The particles existing behind them can face reduced air friction because the preceding particle have moved the air aside. Thus later released

- 42 -

particles catch up with and merge into the earlier released particles. This can cause a chain reaction resulting in the formation of large particles which can not be readily inhaled into the lung - e.g., the formation of particles  
5 having a diameter of more than about 12.0 microns.

A plan view of a simple embodiment of a drug delivery device 40 of the present invention is shown within Figure 4. The device 40 is loaded and operates with a plurality of interconnected disposable containers 1 which  
10 form a package 46. Before describing the details of the individual components of the device 40, a general description of the device and its operation is in order.

Conventional metered dose inhalers and nebulizers suffer from a number of disadvantages. These disadvantages  
15 result in the inability to use these devices to repeatedly deliver the same amount of drug to a patient. The disadvantages are due, in part, to the inability to control particle size - especially when the device is used in diverse environments with greatly different humidity  
20 conditions or when differing amounts of drug are delivered into a fixed amount of air or similar quantities of drug are delivered into differing amounts of air. By adding sufficient energy to the particles to evaporate any carrier particle size is reduced to a uniform minimum and any  
25 humidity variations do not affect particle variability. Further the drug dispensing device of the present invention preferably includes electronic and/or mechanical components which eliminate direct user actuation of drug release. More specifically, the device preferably includes a means  
30 for measuring inspiratory flow rate and inspiratory volume and sending an electrical signal as a result of the simultaneous measurement of both (so that drug can be released at the same point each time) and also preferably includes a microprocessor which is programmed to receive,  
35 process, analyze and store the electrical signal of the

- 43 -

means for measuring flow and upon receipt of signal values within appropriate limits sending an actuation signal to the mechanical means which causes drug to be extruded from the pores of the porous membrane.

5           The device 40 shown in Figure 4 is loaded with a disposable package 46. To use the device 40 a patient (see Figure 3) inhales air from the mouthpiece 30. The air drawn in through the opening 38 (and optionally the desiccator 41) flows through the flow path 29 of the  
10 channel 11. The disposable package 46 is comprised of a plurality of disposable containers 1. Each container 1 includes a drug formulation 5 and is covered by the porous membrane 3. An air-heating mechanism 14 located in the flow path 29. The air heating mechanism 14 is preferably  
15 positioned such that all or only a portion of the air flowing through the path 29 will pass by the heater, e.g., flow vent flaps can direct any desired portion of air through the heater 14. The heat is preferably turned on for 30 sec or less prior to inhalation and turned off after  
20 drug delivery to conserve power.

The device 40 is a hand-held, portable device which is comprised of (a) a device for holding a disposable package with at least one but preferably a number of drug containers, and (b) a mechanical mechanism for forcing the  
25 contents of a container (on the package) through a porous membrane. The device preferably further includes (c) a heating mechanism for adding energy to the air flow into which particles are released, (d) a monitor for analyzing the inspiratory flow of a patient, (e) a switch for  
30 automatically releasing or firing the mechanical means after the inspiratory flow rate and/or volume reaches a predetermined point (f) a means for measuring ambient temperature and humidity and (g) a source of power e.g., conventional batteries.

- 44 -

The device for holding the disposable package may be nothing more than a narrow opening created between two outwardly extending bars 42 and 82 or may include additional components such as one or more wheels, sprockets  
5 or rollers notably mounted on the end(s) of such bars. The rollers may be spring mounted so as to provide constant pressure against the surface(s) of the package. The device may also include a transport mechanism which may include providing drive power to the roller(s) so that when they  
10 are rotated, they move the package from one container to the next. The power source 43 driving the roller(s) is programmed via the microprocessor 26 to rotate the rollers only enough to move the package 39 from one container 1 to the next. In order to use the device 40, the device 40  
15 must be "loaded," i.e. connected to a package 39 which includes drug dosage units having liquid, flowable formulations of pharmaceutically active peptide hormone therein. The entire device 40 is self-contained, light weight (less than 1 kg preferably less than 0.5 kg loaded)  
20 and portable. The power source 43 is preferably in the form of standard alkaline batteries. Two 9 volt batteries could supply the heat required to heat the air which contacts the particles by about 20°C for about 100 doses (see Figures 5 and 6 re energy required).

25 The formulation is preferably heated after the formulation has been forced through the pores of the membrane 3 and aerosolized i.e., energy is preferably added by heating the surrounding air by means of the air-heating mechanism 14 positioned anywhere within the flow path 29.  
30 The amount of energy added by the formulation heating mechanism 45 or air-heating mechanism 5 is controlled by the microprocessor 26 based on the amount of formulation in the container 1 and other factors such as the concentration of the peptide hormone in the formulation and surrounding  
35 humidity. A hygrometer 50 and thermometer 51 are

- 45 -

electrically connected to the microprocessor 26 allowing the amount of heat to be added to be adjusted based on ambient humidity and temperature.

Potent drugs which are highly soluble in water, ethanol and/or mixtures thereof are particularly useful with the present invention in that such drugs can be used. The carrier may be chosen to provide for greater solubility of peptide hormone in the carrier to obtain a high concentration of peptide hormone and thus require less energy to obtain evaporation of the carrier. Particles having a diameter of 6.3 microns can be formed and subjected to evaporation to obtain a particle of one micron in diameter. In the respiratory track this one micron particle would be expected to grow to a 3 micron particle due to moisture added from the high humidity environment of the respiratory tract.

#### Energy For Evaporation

Figure 5 is a graph which can be used in calculating the amount of energy needed to control the size of delivered droplets by controlling the amount of evaporation of carrier from the aerosolized droplets. The graph of Figure 5 contains two types of information, the density of evaporated water vs. temperature and relative humidity, and the cooling of the air as the water evaporates. The four lines that show a rapid increase with temperature portray the density of water vapor in air, at 25, 50, 75, and 100% relative humidity. The 100% relative humidity curve represents the maximum number of milligrams of water that can be evaporated per liter of air. The diagonal lines show the temperature change of the air as the water droplets evaporate (hereafter called the air mass trajectory curves). As the evaporation proceeds, the density and temperature will change by moving parallel to these curves. To calculate these curves, air density of

- 46 -

1.185 grams/liter, air specific heat of .2401 calories/gram, and water latent heat of vaporization of 0.583 cal/mg were assumed. These values imply that a liter of air will cool 2 celsius degrees for every milligram of water evaporated, i.e. evaporating 10 micro-liters will cool a liter of air 20 celsius degrees.

Figure 5 can be used to calculate the amount of preheating needed to evaporate all or substantially all of the carrier in the aerosolized particles. As an example, assume the initial ambient conditions are 25°C and 50% relative humidity. Further, assume that one wants to evaporate 10  $\mu$ l (10mgs) of water from an aqueous drug solution. Finally, assume the final relative humidity is 75%. Under these conditions the aqueous carrier would not evaporate completely. More specifically, the final particles would contain approximately equal amounts of drug and water. To calculate the amount of energy to add for this delivery manoeuver, refer to Figure 5. Locate the point corresponding to 25°C and 50% relative humidity. Move up by 10 milligrams, the amount of water to be evaporated. Now move to the left until the 75% RH curve is crossed. This occurs at about 29°C. These conditions (75% RH and 29°C) represent the condition of the air as delivered to the patient. However, still more energy must be added to make up for the cooling of the air as the water evaporates. To calculate this amount of heat, move parallel to the air mass trajectory curves (downward and to the right) until the initial ambient water vapor density is reached, at approximately 47°C. Thus, sufficient heat to warm the air by 22°C must be added to achieve near complete evaporation.

Figure 6 includes similar information with respect to ethanol which can be used in a similar manner. Figure 5 shows the density of water vapor in air at 25, 50 and 75°C and 100% saturation with the air mass trajectory during



- 47 -

evaporation also shown. The same is shown in Figure 6 for the density of ethanol in air.

The evaporation and growth rates of aqueous droplets is a function of their initial diameter, the amount of drug dissolved therein (concentration) and the ambient relative humidity. The determining factor is whether the water vapor concentration at the surface of the droplet is higher or lower than that of the surrounding air. Because the relative humidity at the surface of a particle (i.e. droplet of aerosolized formulation) is close to 100% for all the high concentration formulations, a five micron droplet will evaporate to a 1 micron dry particle in 0% humidity in less than 20 ms. However, if a particle of drug 1 micron diameter is inhaled into the lungs (99.5% humidity) it will grow to about 3 microns in diameter in approximately one second by accumulating water from the humid lung environment.

#### Desiccator

The opening 38 may have a desiccator 41 positioned therein which desiccator includes a material which removes water vapor from air being drawn into the flow path 29. By reducing or more preferably eliminating water vapor from the air any water in particles of formulation can be more efficiently evaporated. Further, the particles delivered to the patient will have a smaller and more uniform size even if energy is not added to cause evaporation of water from the particles of the formulation.

The device may include a mouth piece 30 at the end of the flow path 29. The patient inhales from the mouth piece 30 which causes an inspiratory flow to be measured by flow sensor 31 within the flow path which path may be, and preferably is, in a non-linear flow-pressure relationship. This inspiratory flow causes an air flow transducer 37 to generate a signal. This signal is conveyed to a

- 48 -

microprocessor which is able to convert, continuously, the signal from the transducer 37 in the inspiratory flow path 29 to a flow rate in liters per minute. The microprocessor 26 can further integrate this continuous air flow rate  
5 signal into a representation of cumulative inspiratory volume. At an appropriate point in the inspiratory cycle, the microprocessor can send a signal to send power from the power source 43 to the air-heating mechanism 14 which uses information from the hygrometer 50, thermometer 51 and  
10 particle size and amount of formulation. The microprocessor also sends a signal to an actuator which causes the mechanical means (e.g., the piston 24) to force drug from a container of the package into the inspiratory flow path 29 of the device and ultimately into the  
15 patient's lungs. After being released, the drug and carrier will pass through a porous membrane 3 to aerosolize the formulation and thereafter enter the lungs of the patient.

When the formulation 5 includes water as all or part  
20 of the carrier it is also desirable to include a desiccator 41 within the flow path 29. The desiccator 41 is preferably located at the initial opening 38 but maybe located elsewhere in the flow path 29 prior to a point in the flow path when the formulation is fired into the flow  
25 path in the form of aerosolized particles. By drawing air through the desiccator 41 water vapor within the air is removed in part or completely. Therefore, only dried air is drawn into the remainder of a flow path. Since the air is completely dried water carrier within the aerosolized  
30 particles will more readily evaporate. This decreases the energy needs with respect to the heating devices 14. The desiccator material can be any compound which absorbs water vapor from air. For example, it may be a compound selected from the group consisting of  $P_2O_5$ ,  $Mg(ClO_4)$ ,  $KOH$ ,  $H_2SO_4$ ,  
35  $NaOH$ ,  $CaO$ ,  $CaCl_2$ ,  $ZnCl_2$ , and  $CaSO_4$ .

- 49 -

Convex/Flexible Porous Membrane

As shown in Figure 3 the convex shape that the flexible membrane 3 takes on during use plays an important role. The membrane may be rigid and convex such as the rigid convex membrane 80 shown in Figure 8. Alternatively, formulation 5 is forced from the container 1 by force applied from a source such as the piston or plate 24 causing the formulation 5 to press against a flexible membrane 3 causing it to convex outward beyond the plan of the resting surface of the membrane 3 and beyond the plan of the inner surface of the channel 11 which is aligned with the surface of membrane 3 when the container 1 is in a drug release position. The convex shape of the membrane 3 is shown in Figure 3. The convex upward distortion of the membrane is important because it positions the pores of the membrane beyond the boundary layer 13 (shown in Figure 3) into faster moving air of the channel 29. A number of containers may be connected together to form a package 46 as is shown in Figure 7. The package 8 is in the form of an elongated tape but can be in any configuration, e.g., circular, square, rectangular, etc.

When pores of the membrane 3 are positioned beyond the boundary layer into the faster moving air of the channel advantages are obtained. Specifically, the (1) formulation exiting the pores is moved to an air stream where it can be readily carried to the patient and (2) the particles formed do not exit into slow moving or "dead" air and thus do not rapidly decelerate to a degree such that particles behind them catch up with, collide into and merge with the particle. Particle collisions are not desirable because they (a) result in particles which are too large and cannot be efficiently inhaled into the lung; and (b) result in an aerosol with diverse and unpredictable particle sizes. Either or both (a) and (b) can result in erratic dosing.

- 50 -

The air-heating mechanism 14 heats the surrounding air within the flow path 29. This causes carrier in the formulation to be evaporated more readily. If sufficient heat is added the only material reaching the patient is the substantially dry peptide hormone drug.

The methodology of the present invention could be carried out with a device that obtains power from a plug-in source. However, the device is preferably a self-contained, hand-held device which is battery powered.

Heating mechanisms of various types can be used. For example, see the heating mechanism in the self-contained, portable sealer for plastic colostomy bags in French patent 2,673,142 which is incorporated herein by reference. A portable heater is also taught in European patent applications 0,430,566 A2 for a "Flavor delivering article" and 0,358,002 for "Smoking articles utilizing electric energy," both of which are incorporated herein by reference to disclose and describe heating components powered by batteries.

Microprocessor 26 of figure 4 includes an external non-volatile read/write memory subsystem, peripheral devices to support this memory system, reset circuit, a clock oscillator, a data acquisition subsystem and an LCD annunciator subsystem. The discrete components are conventional parts which have input and output pins configured in a conventional manner with the connections being made in accordance with instructions provided by the device manufacturers. The microprocessor used in connection with the device of the invention is designed and programmed specifically so as to provide controlled and repeatable amounts of peptide drug to a patient upon actuation. Adjustments can be made in the program so that when the patient's inspiratory flow profile is changed such is taken into consideration. This can be done by allowing the patient to inhale through the device as a test in order

- 51 -

to measure air flow with preferred drug delivery points determined based on the results of several inhalations by each particular patient. This process can be readily repeated when the inspiratory flow profile is changed for  
5 whatever reason, e.g. abdominal incisional pain resulting in low tidal volumes. Determination of optimal drug delivery points in the inspiratory flow can be done at each dosing event, daily, weekly, or with the replacement of a new canister in the device.

10 The microprocessor 26, along with its associated peripheral devices, can be programmed so as to prevent the release of drug from occurring more than a given number of times within a given period of time. This feature makes it possible to prevent overdosing the patient. The overdose  
15 prevention feature can be particularly designed with each individual patient in mind or designed with particular groups of patients in mind.

The microprocessor 26 is programmed so as to allow for monitoring and recording data from the inspiratory flow  
20 monitor without delivering drug. This is done in order to characterize the patient's inspiratory flow profile in a given number of monitoring events, which monitoring events preferably occur prior to dosing events. After carrying out a monitoring event, the preferred point within the  
25 inspiratory cycle for drug delivery can be calculated. This calculated point is a function of measured inspiratory flow rate as well as calculated cumulative inspiratory flow volume. This information is stored and used to allow activation of the valve when the inhalation cycle is  
30 repeated during the dosing event.

#### Drug Delivery Device

The device preferably includes a means for recording a characterization of the inspiratory flow profile for the patient which is possible by including a microprocessor 26

- 52 -

in combination with a read/write memory means and a flow measurement transducer. By using such devices, it is possible to change the firing threshold at any time in response to an analysis of the patient's inspiratory flow profile, and it is also possible to record drug dosing events over time. In a particularly preferred embodiment the characterization of the inspiratory flow can be recorded onto a recording means on the disposable package.

Figure 4 shows a cross-sectional plan view of a hand held, self-contained, portable, breath-actuated inhaler device 40 of the present invention. The device 40 is shown with a holder 20 having cylindrical side walls and a hand grip 21. The holder 20 is "loaded" in that it includes a container 1. A plurality of containers 1 (2 or more) are preferably linked together to form a package 46.

The device is described here largely in connection with a single compartment container as per figures 1 and 2. However, the dual compartment container 70 of figure 14 can be loaded into the device of figure 4 for operation in a similar manner. The difference being that liquid present in one compartment is first moved to the other compartment (mixing takes place) before the formulation is moved out of the porous membrane to form an aerosol. The same means (e.g., a piston or roller) may be used to force the contents out of both compartments or two separate means may be used.

The embodiment shown in Figure 4 is a simple version of the invention. The device 40 may be manually actuated and loaded. More specifically, the spring 22 may be compressed by the user until it is forced down below the actuation mechanism 23. When the user pushes the actuation mechanism 23 the spring 22 is released and the mechanical means in the form of a plate 24 is forced upward against a wall 2 of a container 1. When the container 1 is compressed its contents are forced out through the membrane

- 53 -

3 and aerosolized. Two additional containers 1 shown to the left is unused. The device of Figure 4 would not require the use of low boiling point propellants such as low boiling point fluorocarbons. Numerous additional  
5 features and advantages of the present invention can be obtained by utilizing the monitoring and electronic components described below.

It is important to note that a variety of devices can be used in order to carry out the methodology of the  
10 present invention. However, the device must be capable of aerosolizing drug formulation in a container and preferably does such forcing formulation through a porous membrane with the release point based on pre-programmed criteria which may be mechanically set or electronically set via  
15 criteria readable by the microprocessor 26. The details of the microprocessor 26 and the details of other drug delivery devices which include a microprocessor and pressure transducer of the type used in connection with the present invention are described and disclosed within U.S.  
20 Patent 5,404,871, issued April 11, 1995, entitled "Delivery of Aerosol Medications for Inspiration" which patent is incorporated in its entirety herein by reference, and it is specifically incorporated in order to describe and disclose the microprocessor and program technology used therewith.  
25 The pre-programmed information is contained within a nonvolatile memory which can be modified via an external device. In another embodiment, this pre-programmed information is contained within a "read only" memory which can be unplugged from the device and replaced with another  
30 memory unit containing different programming information. In yet another embodiment, microprocessor 26, containing read only memory which in turn contains the pre-programmed information, is plugged into the device. For each of these three embodiments, changing the programming of the memory  
35 device readable by microprocessor 26 will radically change

- 54 -

the behavior of the device by causing microprocessor 26 to be programmed in a different manner. This is done to accommodate different drugs for different types of treatment.

5           Microprocessor 26 sends signals via electrical connection 27 to electrical actuation device 28 which actuates the means 23 which fires the mechanical plate 24 forcing drug formulation in a container 1 to be aerosolized so that an amount of aerosolized drug is delivered into the  
10           inspiratory flow path 29 when the flexible membrane 3 protrudes outward through the flow boundary layer. A signal is also sent to the heater 14 to add heat energy to the air in the flow path 29. The device 28 can be a solenoid, motor, or any device for converting electrical to  
15           mechanical energy. Further, microprocessor 26 keeps a record of all drug dosing times and amounts using a read/write non-volatile memory which is in turn readable by an external device. Alternatively, the device records the information onto an electronic or magnetic strip on the  
20           package 1. The recorded information can be read later by the care-giver to determine the effectiveness of the treatment. In order to allow for ease of use, it is possible to surround the inspiratory flow path 29 with a mouth piece 30.

25           The electrical actuation means 28 is in electrical connection with the flow sensor 31 which is capable of measuring a flow rate of about 0 to about 800 liters per minute. It should be noted that inhalation flow rates are less than exhalation rates, e.g. max for inhalation 200 lpm  
30           and 800 lpm for exhalation. A variety of different types of flow sensors may be used as per U.S. Patent 5,394,866, issued March 7, 1995, U.S. Patent 5,404,871, issued April 11, 1995 and U.S. Patent 5,450,336, issued September 12, 1995, which are incorporated herein by reference. The flow  
35           sensor 31 includes screens 32, 33 and 34 which are



- 55 -

positioned approximately ¼" apart from each other but may be comprised of a single screen or include a non-linear flow path. It is preferable to include the desiccator 41 at a point prior to the screens 32, 33 and 34 in the flow path so that the elimination of water vapor is considered in any measurement.

Tubes 35 and 36 open to the area between the screens 32, 33 and 34 with the tubes 35 and 36 being connected to a conventional differential pressure transducer 37. Another transducer designed to measure outflow through the opening 38 is also preferably included or the flow sensor 31 is designed so that the same components can measure inflow and outflow. When the user draws air through inspiratory flow path 29, air is passed through the screens 32, 33 and 34 and the air flow can be measured by the differential air pressure transducer 37. Alternatively, other means to measure pressure differential related to air flow, such as a conventional measuring device in the air way, may be used. The flow sensor 31 is in connection with the electrical actuation means 28 (via the connector 39 to the processor 26), and when a threshold value of air flow is reached (as determined by the processor 26), the electrical actuation means 28 fires the release of a mechanical means 23 releasing the plate 24 which forces the release of formulation from a container 1 so that a controlled amount of a peptide hormone is delivered to the patient. The microprocessor 26 is optionally connected to an optionally present vibrating device 45 which may be activated.

### 30 Vibration Device

The vibration device 45 creates ultrasonic vibrations which are preferably at right angles to the plane of the membrane 3. The device 45 may be in the form of a piezoelectric ceramic crystal or other suitable

- 56 -

vibration mechanism. A vibrating device 45 in the form of a piezoelectric crystal may be connected to the porous membrane by means of an attenuator horn or acoustic conduction mechanism, which when correctly matched with the piezoelectric crystal frequency, efficiently transmits ultrasonic oscillations of the piezoelectric crystal to the resonance cavity and the porous polycarbonate membrane and if sized correctly permits the ultrasonic energy to be focused in a polycarbonate membrane 3 allowing for maximum use of the energy towards aerosolizing the liquid formulation 5. The size and shape of the attenuator horn is not of particular importance. It is preferred to maintain a relatively small size in that the device is hand held. The components are chosen based on the particular material used as the porous material, the particular formulation used and with consideration of the velocity of ultrasonic waves through the membrane to achieve a harmonic relationship at the frequency being used.

A high frequency signal generator drives the piezoelectric crystal. This generator is capable of producing a signal having a frequency of from about 575 kilohertz (Khz) to about 32,000 kilohertz, preferably 1,000 to 17,000 kilohertz, more preferably 2,000 to 4,000 kilohertz. The power output required depends upon the amount of liquid being nebulized per unit of time and the area and porosity of the membrane (generally comprised of a polymeric plastic-like material) used for producing the drug dosage unit and/or the efficiency of the connection.

Vibration is applied while the formulation 5 is being forced from the pores of the polycarbonate membrane 3. The formulation can be aerosolized with only vibration i.e., without applying pressure. Alternatively, when vibration is applied in certain conditions the pressure required for forcing the liquid out can be varied depending on the liquid, the size of the pores and the shape of the

- 57 -

pores but is generally in the range of about 50 to 600 psi, preferably 100 to 500 psi and may be achieved by using a piston, roller, bellows, a blast of forced compressed gas, or other suitable device. The vibration frequency used and  
5 the pressure applied can be varied depending on the viscosity of the liquid being forced out and the diameter and length of the openings or pores.

It is desirable to force formulation through the porous membrane with a relatively low pressure e.g.,  
10 pressure less than 500 psi in that lower pressure reduces the chance of breaking the membrane during the release of formulation and makes it possible to make a thinner membrane. The thinner membranes make it easier to make small holes in that the holes or pores of the membrane are  
15 created using a focussed LASER. It is possible to reduce the pressure further by making the holes conical in cross-section. A LASER with a conical focus is used to burn holes through the membrane. The larger diameter of the conical shape is positioned next to the formulation and the  
20 smaller diameter opening is the opening through which the formulation ultimately flows. The ratio of the smaller opening to the diameter of the larger opening is in the range of about 1:2 to about 1:20 i.e., the larger opening is between 2 and 20 times the diameter of the smaller  
25 opening. By creating conical openings wherein the smaller end of the cone has a diameter of less than 6 microns it is possible to produce particles which have a diameter of less than 12 microns and it is also possible to force the formulation through the pores using a pressure of less than  
30 500 psi. The small end of the conical opening preferably has a diameter of less than 3 microns for systemic delivery and less than 5 microns for pulmonary delivery and the pressure used for forcing formulation through the pores is preferable less than 350 psi.

35 When small aerosolized particles are forced into the

- 58 -

air, the particles encounter substantial frictional resistance. This may cause particles to slow down more quickly than desired and may result in particles colliding into each other and combining, which is undesirable with respect to maintaining the preferred particle size distribution within the aerosol. In order to aid in avoiding the particle collision problem, it is possible to include a means by which air flow and the flexible membrane 3 prevent collisions. Specifically, the patient inhales thereby creating an air flow toward the patient over the protruding membrane 3. The air flow carries the formed particles along and aids in preventing their collision with each other. The shape of the container opening, the shape of the membrane covering that opening, as well as the positioning and angling of the flow of air through the channel 11 relative to the direction of formulation exiting the pores of the membrane 3 can be designed to aid in preventing particle collision. It is desirable to shape the opening and matching membrane so as to minimize the distance between any edge of the opening and the center of the opening. Accordingly, it is not desirable to form a circular opening which would maximize the distance between the outer edges of the circle and the center of the circle, whereas it is desirable to form an elongated narrow rectangular opening covered by a rigid membrane 80 as shown in Figure 8. Using such a configuration makes it possible to better utilize the air flow relative to all of the particles of formulation being forced from the pores of the membrane 3. When a circular opening is used, particles which are towards the center of the circle may not be carried along by the air being drawn over the membrane 3 and will collide with each other. The elongated rectangle could be formed in a circle, thereby providing an annular opening and air could be forced outward from the outer and inner edges of the circle formed. Further details

- 59 -

regarding such are described in U.S. patent application Serial No. 08/247,012, filed May 20, 1994 which is incorporated herein by reference to disclose and describe such.

#### 5 Operation of the Device 40

The device of Figure 4 shows all of the components present within the single, hand-held, portable breath actuated device, e.g. the microprocessor 26 and flow sensor 31 used to provide the electronic breath actuated release  
10 of drug. The device of Figure 4 includes a holding means and mechanical means and preferably operates electronically, i.e. the actuation means is preferably not directly released by the user. The patient inhales through inspiratory flow path 29 which can form a mouth piece 30.  
15 Air enters the device via the opening 38. The inhaling is carried out in order to obtain a metering event using the differential pressure transducer 37. Further, when the inspiratory flow meets a threshold of a pre-programmed criteria, the microprocessor 26 sends a signal to an  
20 actuator release electrical mechanism 28 which actuates the mechanical means 23, thereby releasing a spring 22 and plate 24 or equivalent thereof, forcing aerosolized formulation into the channel 11, and out of the membrane 3 into the flow path 29 where the air surrounding the  
25 particles is optionally heated by the air heater 14. Further details regarding microprocessors 26 of Figure 4 are described within U.S. Patent 5,394,866, issued March 7, 1995, entitled "An Automatic Aerosol Medication Delivery System and Methods", which is incorporated herein by  
30 reference in its entirety and specifically incorporated in order to describe and disclose flow measurements, the microprocessor and program technology used therewith.

Microprocessor 26 of Figure 4 includes an external non-volatile read/write memory subsystem, peripheral

- 60 -

devices to support this memory system, reset circuit, a clock oscillator, a data acquisition subsystem and a visual annunciator subsystem. The discrete components are conventional parts which have input and output pins  
5 configured in a conventional manner with the connections being made in accordance with instructions provided by the device manufacturers. The microprocessor used in connection with the device of the invention is designed and programmed specifically so as to provide controlled and  
10 repeatable amounts of peptide hormone to a patient upon actuation. The microprocessor must have sufficient capacity to make calculations in real time. Adjustments can be made in the program so that when the patient's inspiratory flow profile is changed such is taken into  
15 consideration. This can be done by allowing the patient to inhale through the device as a test (monitoring event) in order to measure air flow with preferred drug delivery points determined based on the results of several inhalations by each particular patient. This process can  
20 be readily repeated when the inspiratory flow profile is changed for whatever reason. When the patient's lung function has decreased the program will automatically back down in terms of the threshold levels required for release of drug. This "back down" function insures drug delivery  
25 to a patient in need but with impaired lung function. Determination of optimal drug delivery points in the inspiratory flow can be done at each dosing event, daily, weekly, or with the replacement of a new cellular array in the device.

30 The microprocessor 26 of the present invention, along with its associated peripheral devices, can be programmed so as to prevent triggering the actuation mechanism 28 more than a given number of times within a given period of time. This feature makes it possible to  
35 prevent overdosing the patient. The overdose prevention

- 61 -

feature can be particularly designed with each individual patient in mind or designed with particular groups of patients in mind. For example, the microprocessor can be programmed so as to prevent the release of more than  
5 approximately 30 mg of peptide hormone per day when the patient is normally dosed with approximately 25 mg of peptide hormone drug per day. The device can be designed to switch off this lock-out function so that peptide hormone can be delivered in an emergency situation.

10 The systems can also be designed so that only a given amount of peptide hormone drug is provided at a given dosing event. For example, the system can be designed so that only approximately 10  $\mu$ g of peptide hormone drug is given in a given 15-minute period over which the patient  
15 will make approximately 10 inhalations with 1  $\mu$ g of drug being delivered with each inhalation. By providing this feature, greater assurances are obtained with respect to delivering the peptide hormone drug gradually over time and thereby carrying out endocrine therapy without overdosing  
20 the patient.

The microprocessor 26 of the invention can be connected to external devices permitting external information to be transferred into the microprocessor of the invention and stored within the non-volatile read/write  
25 memory available to the microprocessor. The microprocessor of the invention can then change its drug delivery behavior based on this information transferred from external devices. All of the features of the invention are provided in a portable, programmable, battery-powered, hand-held  
30 device for patient use which has a size which compares favorably with existing metered dose inhaler devices.

The microprocessor 26 of the present invention is programmed so as to allow for monitoring and recording data from the inspiratory flow monitor without delivering drug.  
35 This is done in order to characterize the patient's

- 62 -

inspiratory flow profile in a given number of monitoring events, which monitoring events preferably occur prior to dosing events. After carrying out a monitoring event, the preferred point within the inspiratory cycle for drug  
5 delivery can be calculated. This calculated point is a function of measured inspiratory flow rate as well as calculated cumulative inspiratory flow volume. This information is stored and used to allow activation of the electronic actuation means when the inhalation cycle is  
10 repeated during the dosing event.

#### Method of Administration

The method and device of the invention provides a number of features which make it possible to achieve the controlled and repeatable dosing procedure required for the  
15 endocrine therapy with peptide hormones with a low therapeutic index. First, the membrane is permanently convex or is flexible and protrudes into fast moving air aiding the elimination of particle collisions. Second, the invention makes it possible to eliminate any carrier from  
20 the aerosolized particles and provide substantial dry peptide hormone particles to a patient which particles can be manufactured to have a uniform size. By delivering particles of uniform size repeatability of dosing is enhanced regardless of the surrounding environment, e.g.  
25 different humidity conditions. Third, the device makes it possible to administer drug at the same point with respect to inspiratory flow rate and inspiratory volume at each drug delivery point thereby improving repeatability of dosing.

30 The method of the invention involves the release of a liquid, flowable peptide hormone formulation from individual disposable containers which may be interconnected in a package. This is desirable in that the liquid, flowable drug is packaged under a sterile



- 63 -

environment and therefore does not require and preferably does not include additional materials such as antifungal, bacteriostatics, and preservatives which would normally be required in a liquid formulation if the formulation was to  
5 be opened, exposed to air, closed and later used again. A new container and membrane are used for each release of drug. Thus, the membrane and container are disposable thereby preventing clogging of pores which takes place with reuse. The invention does not require the use of low  
10 boiling point propellants such as low boiling point fluorocarbons. The use of such low boiling point propellants in conventional metered dose inhaler devices is desirable because such propellants eliminate the need for preservatives, antifungal and bacteriostatic compounds.  
15 However, there are potential environmental risks to using low boiling point fluorocarbons. Accordingly, the present invention provides potential environmental benefits and would be particularly useful if government regulations prevented further use of devices which dispensed low  
20 boiling point fluorocarbons.

In addition to environmental advantages, the present invention offers advantages due to the relatively slow speed at which the aerosol dispersion is delivered to the patient. A conventional metered dose inhaler device  
25 discharges the aerosol outward at a relatively high rate of speed which causes a large amount of the aerosol particles to make contact with the inside of the patient's mouth and the back of the patient's throat. This decreases the amount of drug actually administered to the patient's lungs  
30 as compared with the present system, wherein the aerosol is delivered at a relatively slow rate of speed and can be inhaled slowly by the patient.

The method preferably uses a drug delivery device which is not directly actuated by the patient in the sense  
35 that no button is pushed nor valve released by the patient

- 64 -

applying physical pressure. On the contrary, the device of the invention provides that the actuation mechanism which causes drug to be forced from a container is fired automatically upon receipt of a signal from a microprocessor programmed to send a signal based upon data  
5 received from a monitoring device such as an airflow rate monitoring device. A patient using the device withdraws air from a mouthpiece and the inspiratory rate, and calculated inspiratory volume of the patient is measured  
10 simultaneously one or more times in a monitoring event which determines an optimal point in an inhalation cycle for the release of a dose of any desired drug. Inspiratory flow is preferably measured and recorded in one or more monitoring events for a given patient in order to develop  
15 an inspiratory flow profile for the patient. Recorded information is preferably analyzed by the microprocessor in order to deduce a preferred point within the patient's inspiratory cycle for the release of drug with the preferred point being calculated based on the most likely  
20 point to result in a reproducible delivery event.

A flow rate monitoring device continually sends information to the microprocessor, and when the microprocessor determines that the optimal point in the respiratory cycle is reached, the microprocessor actuates  
25 a component which fires a mechanical means (and activates the vibration device) which causes drug to be forced out of the container and aerosolized. Accordingly, drug is repeatedly delivered at a pre-programmed place in the inspiratory flow profile of the particular patient which is  
30 selected specifically to maximize reproducibility of drug delivery and peripheral deposition of the drug. It is pointed out that the device of the present invention can be used to, and actually does, improve the efficiency of drug delivery. However, this is not the most important feature.  
35 A more important feature is the reproducibility of the

- 65 -

release of a tightly controlled amount of drug (with a narrow range of particle size) repeatedly at the same particular point in the respiratory cycle so as to assure the delivery of a controlled and repeatable amount of drug  
5 to the lungs of each individual patient, i.e. intrapulmonary drug delivery with tightly controlled dosing.

The heating component(s) and/or the desiccator to remove water vapors aid in providing repeatability in  
10 dosing in that the particles reaching the patient will have the same size regardless of the surrounding humidity. By keeping the particle size the same at each dosing event the particles deposit at the same general area of the lung at each event. These features improve repeatability along  
15 with automatic control of the drug release mechanism, combined with frequent monitoring events in order to calculate the optimal flow rate and time for the release of drug. Further, the particles will have uniform size in that all carrier is removed regardless of the humidity of the  
20 surrounding environment. Because the drug release mechanism is fired automatically and not manually, it can be predictably and repeatedly fired at that same point in the inspiratory cycle. Because dosing events are preferably preceded by monitoring events, the point in the  
25 inspiratory cycle of the release can be readjusted based on the particular condition of the patient. For example, patients suffering from asthma have a certain degree of pulmonary insufficiency which may well change with the administration of drug. These changes will be taken into  
30 account in the monitoring event by the microprocessor which will readjust the point of release of the drug in a manner calculated to provide for the administration of an amount of peptide hormone to the patient presently needed by the patient at each dosing event.

- 66 -

When administering drug using the inhalation device of the present invention, the entire dosing event can involve the administration of anywhere from 10  $\mu$ l to 1,000 ml of drug formulation, but more preferably involves the administration of approximately 50  $\mu$ l to 10,000  $\mu$ l of drug formulation. Very small amounts of drug (e.g., nanogram amounts) may be dissolved or dispersed within a pharmaceutically acceptable, liquid, excipient material to provide a liquid, flowable formulation which can be readily aerosolized. The container will include the formulation having drug therein in an amount of about 10 ng to 300  $\mu$ g, more preferably about 50  $\mu$ g. The large variation in the amounts which might be delivered are due to different drug potencies and different delivery efficiencies for different devices, formulations and patients. The entire dosing event may involve several inhalations by the patient with each of the inhalations being provided with drug from the device. For example, the device can be programmed so as to release the contents of a single container or to move from one container to the next on a package of interconnected containers. Delivering smaller amounts from several containers can have advantages. Since only small amounts are delivered from each container and with each inhalation, even a complete failure to deliver drug with a given inhalation is not of great significance and will not seriously disturb the reproducibility of the dosing event. Further, since relatively small amounts are delivered with each inhalation, the patient can safely administer a few additional mg of peptide hormone without fear of overdosing.

In addition to drug potency and delivery efficiency, drug sensitivity must be taken into consideration. The present invention makes it possible to vary dosing over time if sensitivity changes and/or if user compliance and/or lung efficiency changes over time.

- 67 -

Based on the above, it will be understood that the dosing or amount of peptide hormone actually released from the device can be changed based on the most immediately prior monitoring event wherein the inspiratory flow of a patient's inhalation is measured.

Variations in doses are calculated by monitoring the effect of one or more lung function parameters in response to known amounts of respiratory drug released from each container and delivered to the patient. If the response in changing measured lung function parameters is greater than with previous readings, then the dosage (number of containers released) is decreased or the minimum dosing interval is increased. If the response in changing measured lung function parameters is less than with previous readings, then the dosing amount is increased or the minimum dosing interval is decreased. The increases and decreases are gradual and are preferably based on averages (of 10 or more readings of lung function parameter after 10 or more dosing events) and not a single dosing event and monitoring event. The preferred drug delivery device of the present invention can record dosing events and lung function parameters over time, calculate averages and deduce preferred changes in administration of peptide hormone.

One of the important features and advantages of the present invention is that the microprocessor can be programmed to take a number of different criteria into consideration with respect to dosing times. For example, the microprocessor can be programmed so as to include a minimum time interval between doses i.e. after a given delivery another dose cannot be delivered until a given period of time has passed. Secondly, the timing of the device can be programmed so that it is not possible to exceed the administration of a set maximum amount of drug within a given time. For example, the device could be

- 68 -

programmed to prevent dispersing more than ten mg of peptide hormone within one hour. More importantly, the device can be programmed to take both criteria into consideration. Thus, the device can be programmed to  
5 include a minimum time interval between doses and a maximum amount of drug to be released within a given time period. For example, the microprocessor could be programmed to allow the release of a maximum of ten mg of peptide hormone during an hour which could only be released in amounts of  
10 one mg with each release being separated by a minimum of five minutes.

The dosing program can be designed with some flexibility. For example, if the patient normally requires 25 mg per day of peptide hormone, the microprocessor can be  
15 programmed to provide a warning after 25 mg have been administered within a given day and to continue the warning thereafter to alert the user of possible overdoses. By providing a warning and not a lock-out, the device allows for the patient to administer additional peptide hormone,  
20 if needed, due to a decreased lung function, abdominal pain, account for misdelivery of peptide hormone such as due to coughing or sneezing during an attempted delivery.

The ability to prevent overdosing is a characteristic of the device due to the ability of the  
25 device to monitor the amount of peptide hormone released and calculate the approximate amount of peptide hormone delivered to the patient based on monitoring a variety of lung function parameters. The ability of the present device to prevent overdosing is not merely a monitoring  
30 system which prevents further manual actuation of a button. As indicated above, the device used in connection with the present invention is not manually actuated, but is fired in response to an electrical signal received from a microprocessor (which received data from a monitoring  
35 device such as a device which monitors inspiratory flow)

- 69 -

and allows the actuation of the device upon achieving an optimal point in a inspiratory cycle. When using the present invention, each actuation of the device will administer drug to the patient in that the device is fired  
5 in response to patient inhalation. More specifically, the preferred embodiment of the device does not allow for the release of peptide hormone drugs merely by the manual actuation of a button to fire a burst of peptide hormone drugs into the air or a container.

10 A variety of different embodiments of the dispersion device of the invention are contemplated. In accordance with one embodiment it is necessary to carry out manual cocking of the device. This means that energy is stored such as by retracting a spring so that, for example, a  
15 piston can be positioned below the drug containing container. In a similar manner a piston connected to a spring can be withdrawn so that when it is released it will force air through the air dispersion vents. Automatic cocking of forced storing systems for both the drug  
20 formulation and the air flow may be separate or in one unit. Further, one may be manual whereas the other may be done automatically. In accordance with one embodiment the device is cocked manually but fired automatically and electronically based on monitoring the patients inspiratory  
25 flow. The formulation may be physically moved through the porous membrane in a variety of different ways. Formulation may be forced through the membrane by a piston or, without applying force to the formulation, the membrane being vibrated at frequencies sufficient to create an  
30 aerosol.

The microprocessor 26 of the present invention preferably includes a timing device. The timing device can be electrically connected with visual display signals as well as audio alarm signals. Using the timing device, the  
35 microprocessor can be programmed so as to allow for a

- 70 -

visual or audio signal to be sent when the patient would be normally expected to administer peptide hormone drugs. In addition to indicating the time of administration (preferably by audio signal), the device can indicate the amount of peptide hormone drugs which should be administered by providing a visual display. For example, the audio alarm could sound alerting the patient that peptide hormone drugs should be administered. At the same time, the visual display could indicate "one dosage unit" as the amount of drug (number of containers) to be administered. At this point, a monitoring event could take place. After completion of the monitoring event, administration would proceed and the visual display would continually indicate the remaining amount of peptide hormone drugs which should be administered. After the predetermined dose (indicated number of containers) had been administered, the visual display would indicate that the dosing event had ended. If the patient did not complete the dosing event by administering the stated amount of drug, the patient would be reminded of such by the initiation of another audio signal, followed by a visual display instructing the patient to continue administration.

Additional information regarding dosing peptide hormone drugs can be found within Harrison's - Principles of Internal Medicine (most recent edition) and the Drug Evaluation Manual, 1993 (AMA-Division of Drugs and Toxicology), both of which are published by McGraw Hill Book Company, New York, incorporated herein by reference to disclose conventional information regarding dosing of peptide hormone drugs.

#### Operation of Delivery Device

The device 40 schematically shown within Figure 4 can be specifically operated as follows. A container 1 is



- 71 -

loaded into the device 6. The device is then armed meaning that the piston such as the spring-loaded piston 24 is cocked. If applicable another piston (not shown) used to compress the liquid formulation in a dual container system is cocked. Further, a container 1 of the package is moved into position and any cover is stripped off of the porous membrane 3. Thereafter, the patient withdraws air from the mouthpiece 30 and the patient's inhalation profile is developed using the microprocessor 26. After the inhalation profile is determined, the microprocessor calculates a point within the inhalation profile at which the drug should be released in order to maximize repeatability of the dosing, e.g. by plotting a curve of breath velocity versus time and determining the point on the curve most likely to provide repeatability of dosing. However, in order to carry out methodology in accordance with the present invention it is not necessary to plot any curve of breath velocity versus time. The device can be set so that the dose will be repeatedly released at approximately the same point with respect to inspiratory flow rate and inspiratory volume. If the device repeatedly fires at the same inspiratory flow rate and inspiratory volume each time the patient will receive substantially the same dose. Both criteria must be measured and used for firing to obtain repeatability.

Further details with respect to obtaining improved repeatability of dosing in addition to improved delivery efficiency are disclosed within related application entitled: "Intrapulmonary Drug Delivery Within Therapeutically Relevant Inspiratory Flow/Volume Values" filed on July 11, 1994, U.S. Serial No. 08/273,375 which application is incorporated herein by reference. The microprocessor of the present invention can be programmed to release drug based on all or any of the following parameters.

- 72 -

(1) Delivery should be at an inspiratory flow rate inside a range of about 0.10 to about 2.0 liters per second (efficiency can be obtained by delivering at a flow rate in a range of 0.2 to about 1.8 liters per second and more preferably 0.15 to 1.7 liters per second). Repeatability of the delivery is obtained by releasing at substantially the same inspiratory flow rate at each drug release.

(2) Delivery should be at a point within a patient's inspiratory volume of about 0.15 to about 2.0 liters (further efficiency of delivery can be obtained by delivering within a range of 0.15 to 0.8 liters and more preferably 0.15 to about 0.4 liters). Repeatability of delivery is obtained by delivering at the same inspiratory volume at each release of drug.

(3) Delivery is improved by providing a system which creates particles for systemic delivery wherein the particles are in the range of about 0.5 to about 12.0 microns, preferably 0.5 to 6 microns and more preferably 0.5 to about 3 microns.

(4) It is desirable to have obtained a concentration of the drug in the carrier in the range of from about 0.01 to about 12.5% preferably 0.1 to 10%. By maintaining the concentration of drug to carrier in this range it is possible to create particles which are somewhat larger than would be desirable for delivery but to reduce those particles in size by evaporation of carrier.

(5) Air drawn into the flow path of the aerosolized particles is heated by adding energy to each 10  $\mu$ l of formulation in an amount of about 20 Joules to 100 Joules, more preferably 20 Joules to 50 Joules. The heated air aids in reducing the effect of humidity and evaporates carrier away from the particles thereby providing smaller particles for inhalation.

(6) Air is added to the aerosolized formulation by the patient drawing air into the aerosolized mist in an

- 73 -

amount of about 100 milliliters to 2 liters per 10 microliters of aerosol formulation.

(7) Vibration may be created on the porous membrane in an amount 575 to 32,000, preferably 1,000 to 17,000 and 5 more preferably 2,000 to 4,000 kilohertz.

(8) The pore size of the membrane is regulated within a range of 0.25 to about 6.0 microns, preferably 0.5 to 3 microns and more preferably 1 to 2 microns. This size refers to the diameter of the pore through which the  
10 formulation exits the membrane. The diameter of the opening into which the formulation flows may be 2 to 20 times that size in diameter thereby providing a conical configuration.

(9) The viscosity of the formulation affects the  
15 amount of pressure which needs to be applied to force the formulation through the pores and should be within the range of 25% to 1,000% the viscosity of water.

(10) The extrusion pressure is regulated within a range of 50 to 600 psi more preferably 100 to 500 psi.  
20 Lower pressures may be obtained by using the conical configuration for the pore size.

(11) The microprocessor should also be provided information regarding the ambient temperature and atmospheric pressure. The temperature is preferably close  
25 to room temperature i.e., within a range of 15°C to 30°C. An atmospheric pressure is generally 1 atmosphere or slightly lower at higher altitudes, e.g., about 75% of 1 atmosphere.

(12) To provide for consistency in dosing the ratio  
30 of the carrier to drug should be maintained constant and more highly soluble drugs are more desirable. However, it is possible to use drugs that are insoluble by creating suspensions or by using solubility enhancers.

(13) A desiccator is preferably used to remove water  
35 vapor from air drawn into the flow path by the patient.

- 74 -

(14) The pores are preferably placed in the porous membrane in an elongated oval or elongated rectangular configuration. By configuring the pores in this manner and drawing air perpendicularly over the narrower dimension of the configuration it is possible to reduce the amount of collisions between particles and thereby avoid particles collision resulting in accumulation.

(15) The thickness of the membrane is preferably regulated in the range of 5 to 200 microns or more preferably 10 to 50 microns. Thinner membranes are useful in that less pressure is required to force formulation through the membrane. The membrane has a tensile strength of 5,000 to 20,000, preferably 8,000 to 16,000 and more preferably 14,000 to 16,000 psi.

(16) The membrane is configured so as to have a convex configuration which protrudes into faster moving air created by the patient's inhalation or is designed to be flexible so that it will assume a convex configuration when formulation is forced through the membrane.

(17) After the microprocessor is provided information with respect to above parameters or measurements a drug release point is chosen the microprocessor will continually return to substantially the same firing point at each drug delivery so as to obtain repeatability of dosing.

After drug has been delivered it is possible to discontinue any readings with respect to flow and/or volume. However, it is preferable to continue readings with respect to both criteria after drug has been released. By continuing the readings the adequacy of this patient's particular drug delivery maneuver can be determined. All of the events are recorded by the microprocessor. The recorded information can be provided to the caregiver for analysis. For example, the caregiver can determine if the patient correctly carried out the inhalation maneuver in

- 75 -

order to correctly delivery drug and can determine if the patient's inhalation profile is effected by the drug.

The package 70 of figure 14 includes a first container 71 and a second container 72. The containers 71 and 72 are in fluid connection with each other but the fluid connection is interrupted by a membrane 73 which membrane can be ruptured by the application of pressure in an amount of about 50 psi or less. A device such as the component 74 forces against the bottom of the container 72 and forces the contents 75 (which is liquid) against the membrane 73 which is then ruptured. The liquid 75 then enters the container 71 and mixes with the dry powder 76 present with the container 71. The container 71 may include mixing components 77 and 78. These components may be vibrating devices, ultrasonic devices or other suitable mechanisms allowing for the mixing of the liquid with the dry peptide. When the mixing is completed the component 79 is forced against the container 71 forcing the peptide drug formulation present therein into the chamber 80. Once the formulation is in the chamber 80 it is there under pressure and can be moved through the membrane 81 by the application of that pressure and/or by the use of a vibrating device 82. The formulation is moved through the membrane 81 only after removal of the cover sheet 83.

The membrane 81 includes pores having a diameter in the range of about 0.25 micron to about 6 microns and a pore density in the range of  $1 \times 10^4$  to about  $1 \times 10^8$  pores per square centimeter. The porous membrane 81 is preferably comprised of a material having a density in the range of about 0.25 to 3.0 mg/cm<sup>2</sup>, more preferably about 1.7 mg/cm<sup>2</sup> and a thickness of about 2 to about 20 microns, more preferably 8 to 12 microns. The liquid 75 present in the container 72 is preferably capable of dissolving the peptide component 76. The peptide powder 76 is preferably completely dissolved within the container 71 prior to being

- 76 -

forced into the chamber 80. Dissolving the peptide makes it easier to move the peptide through the pores of the membrane 81 and create a fine mist aerosol. Keeping the dried peptide powder apart from the liquid makes it  
5 possible to maintain a longer shelf life.

The instant invention is shown and described herein in which is considered to be the most practical and preferred embodiments. It is recognized, however, that the departures may be made therefrom which are within the scope  
10 of the invention and that obvious modifications will occur to one skilled in the art upon reading this disclosure.

- 77 -

CLAIMS

WHAT IS CLAIMED IS:

- 1           1.   A peptide hormone drug delivery device,  
2 comprising:  
3           a channel having a first opening into which air  
4 can be inhaled, a second opening from which a patient can  
5 withdraw air and a third opening positioned between the  
6 first and second openings;  
7           a disposable, dual compartment container,  
8 comprising;  
9           a first compartment having therein dry peptide  
10 hormone drug, the first compartment having an opening  
11 therein which is covered by a flexible porous membrane with  
12 pores having a diameter of about 0.25 micron to about 6  
13 microns, the membrane positioned at the third opening of  
14 the channel; and  
15           a second compartment having a flowable liquid  
16 therein connected to and in fluid connection with the first  
17 compartment, the fluid connection being interrupted by a  
18 membrane which is ruptured by the application of pressure;  
19           a means for applying force to the dual compartment  
20 container such that fluid in the second container is forced  
21 into the first container and out of the porous membrane;  
22           wherein the device is a hand-held self-  
23 contained device having a total weight of 1 kilogram or  
24 less.
- 1           2.   The drug delivery device of claim 1, wherein a  
2 single means is used for applying physical force to the  
3 first compartment and the second compartment.

- 78 -

1           3.    The drug delivery device of claim 1, further  
2 comprising:

3           a hygrometer for measuring ambient humidity, the  
4 hygrometer supplying information used to determine an  
5 amount of energy to be added by the air-heating device.

1           4.    The drug delivery device of claim 1, further  
2 comprising:

3           an air heating device which heats air drawn into the  
4 channel.

1           5.    The drug delivery device of claim 4, wherein  
2 the opening in the first compartment forms an open channel  
3 leading from the opening to a breakable seal beyond which  
4 is an area covered by the flexible porous membrane.

1           6.    The drug delivery device of claim 4, wherein  
2 the pores have a cross-sectional configuration with a small  
3 end opening of 0.25 to 6.0 microns in diameter and a large  
4 end opening of 2 to 20 times the diameter of the small end.

1           7.    The drug delivery device of claim 1, further  
2 comprising:

3           a means for measuring airflow through the channel  
4 and determining inspiratory flow rate and inspiratory  
5 volume; and

6           a means for determining a beginning point to force  
7 formulation through the pores of the membrane based on real  
8 time values of inspiratory flow rate and inspiratory  
9 volume.

1           8.    The drug delivery device of claim 7, wherein  
2 the measuring means is mechanical.



- 79 -

1           9.    The drug delivery device of claim 7, wherein  
2 the measuring means is electronic.

1           10.   The drug delivery device of claim 1, further  
2 comprising:

3           a desiccator in the channel.

1/7

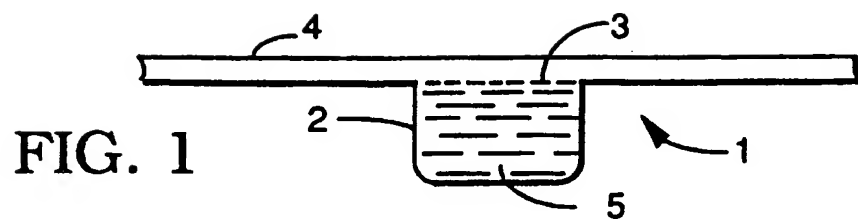


FIG. 1

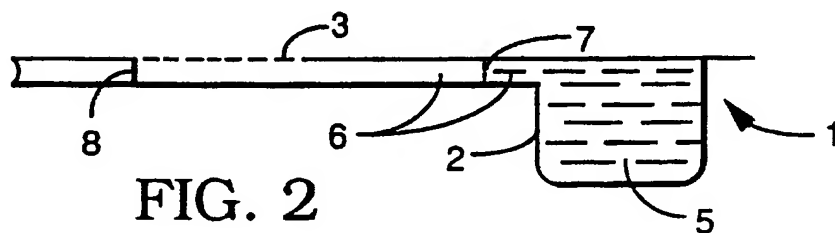


FIG. 2

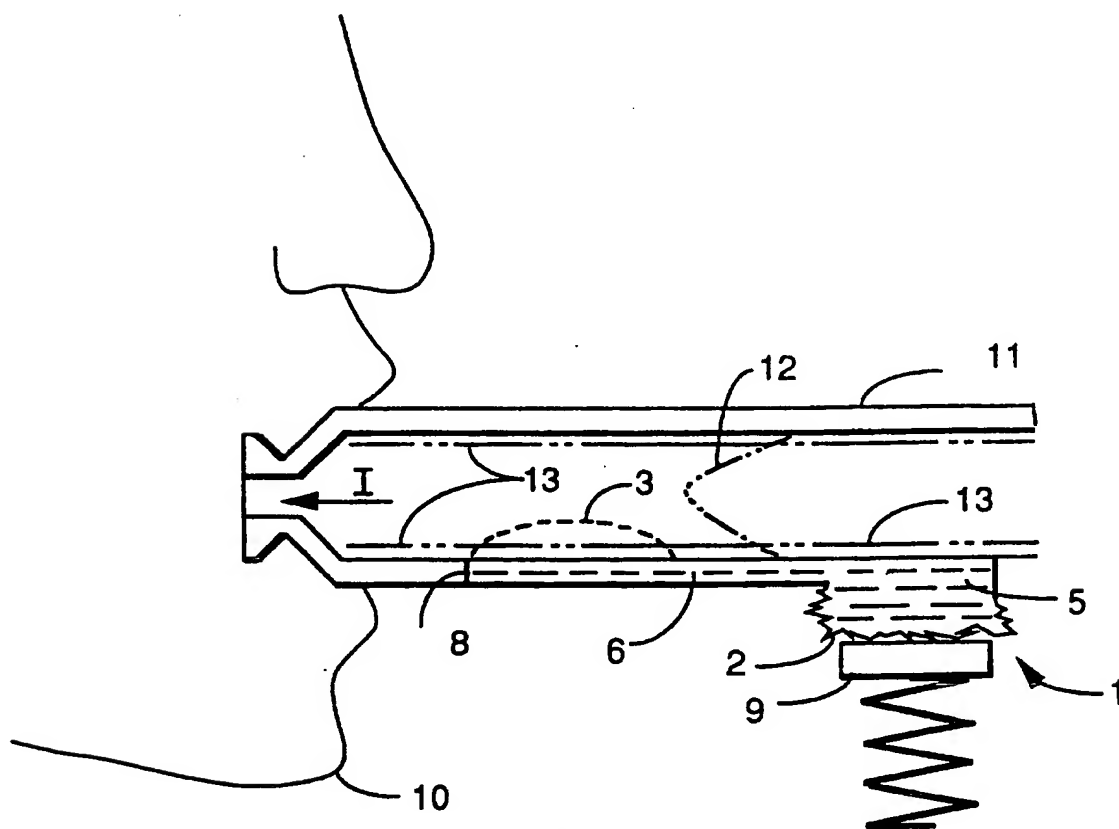
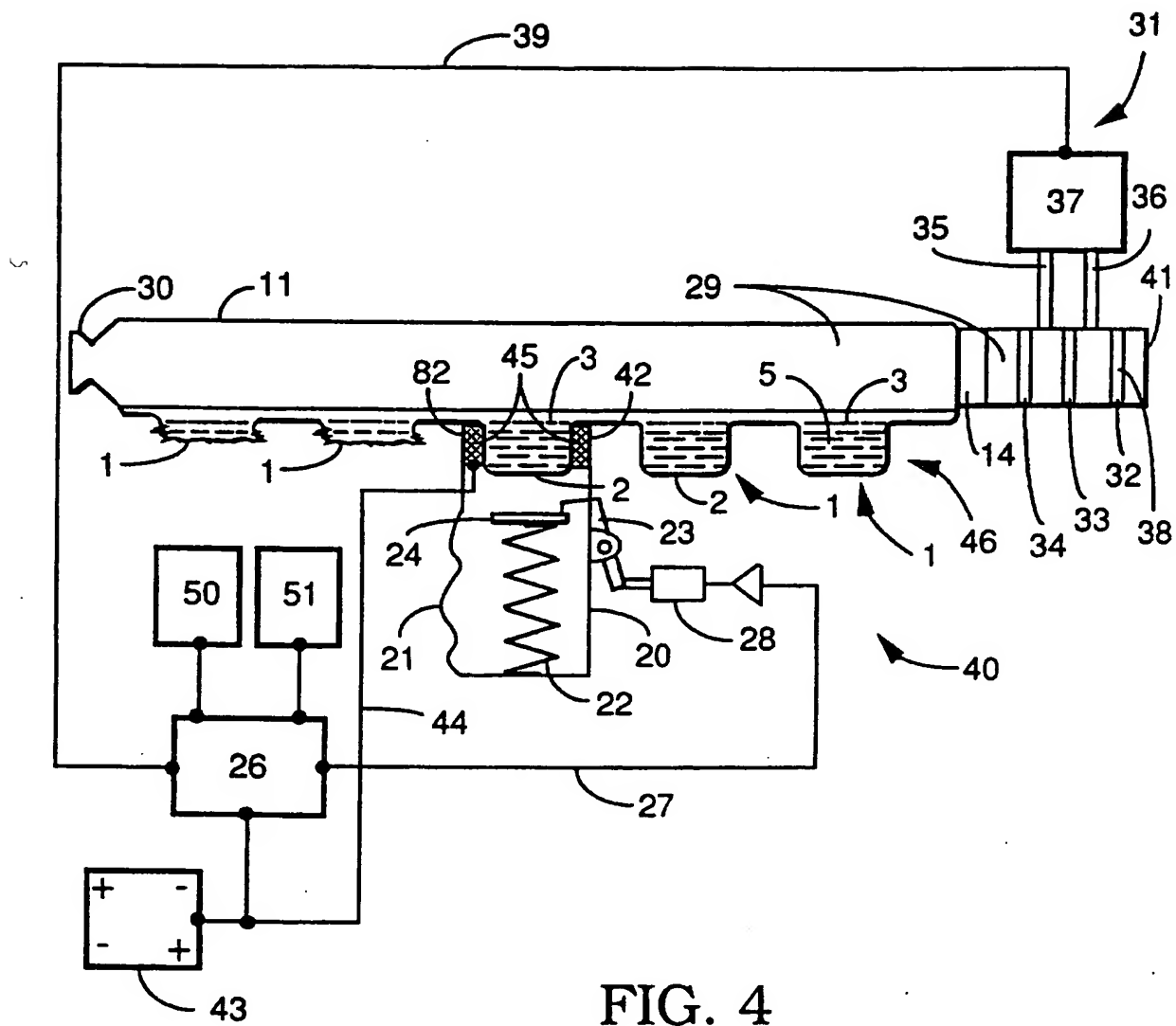


FIG. 3



3/7

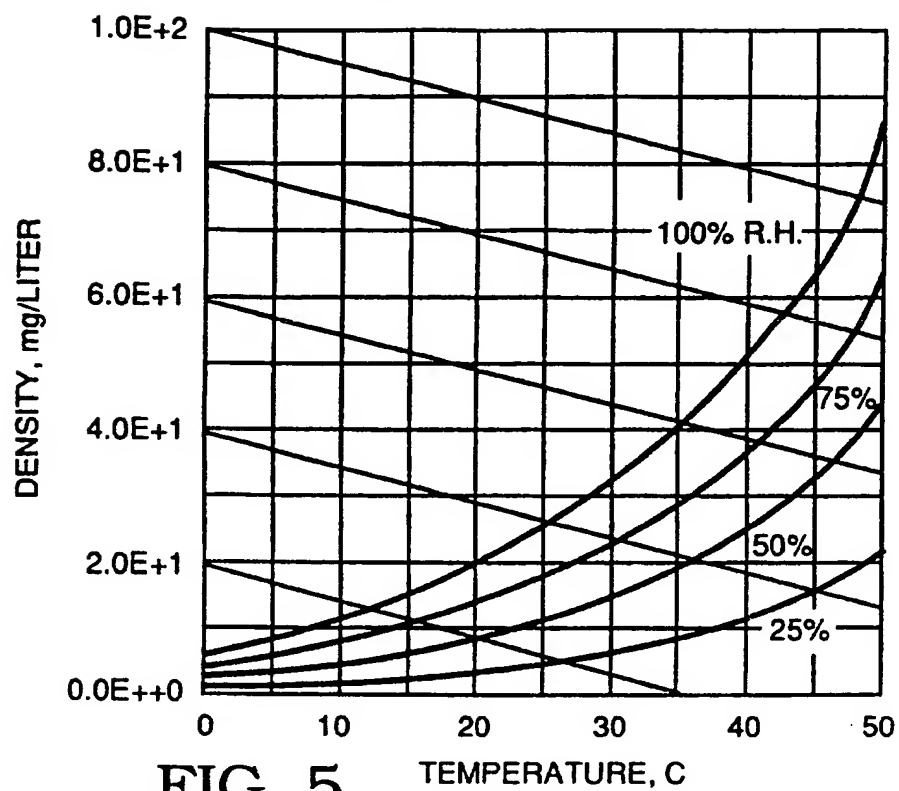


FIG. 5

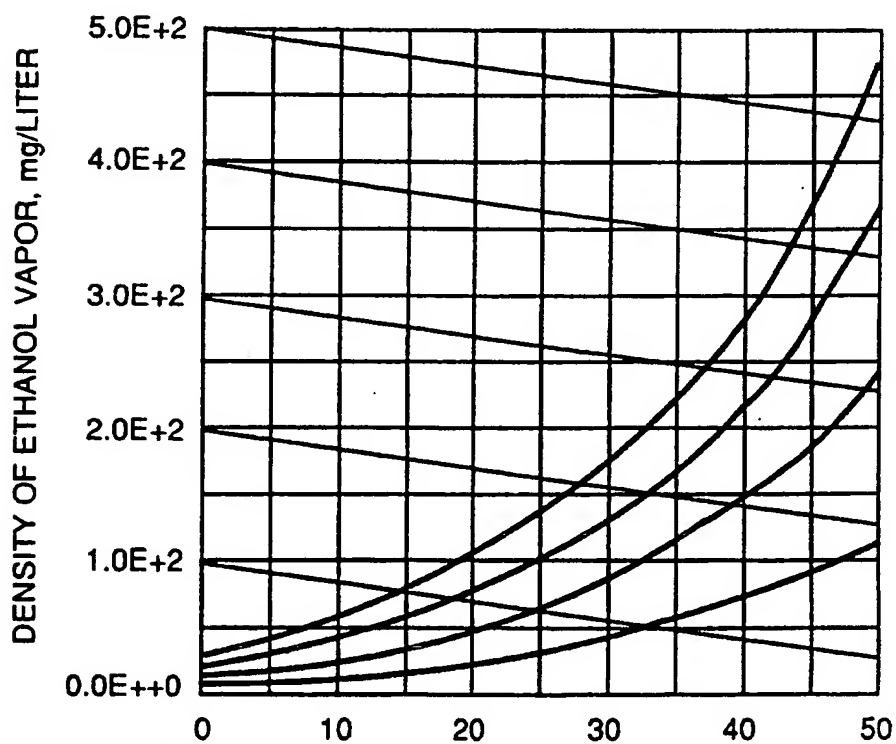


FIG. 6

TEMPERATURE, C

SUBSTITUTE SHEET (RULE 26)

4/7

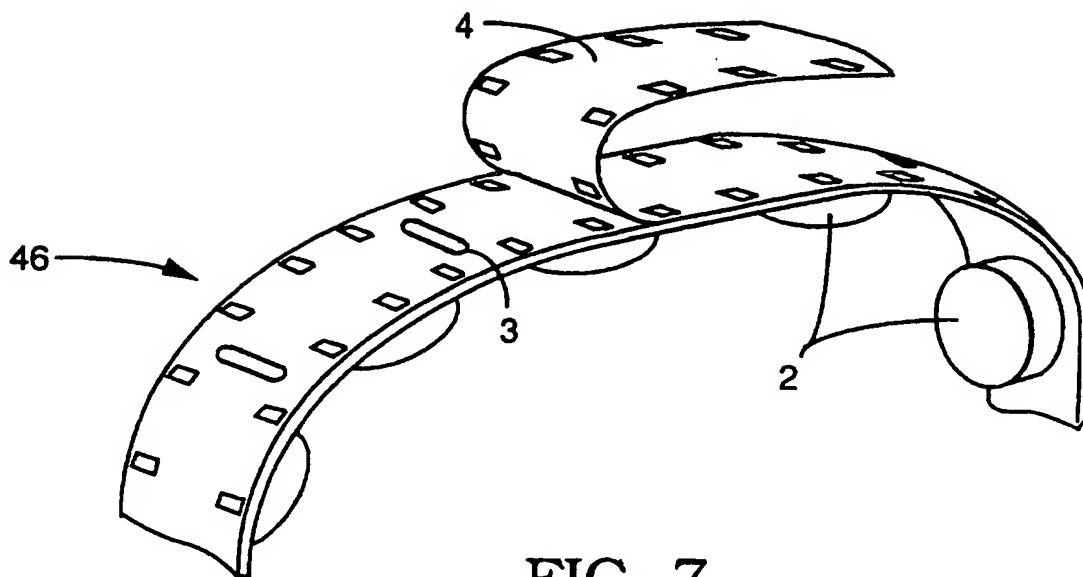


FIG. 7

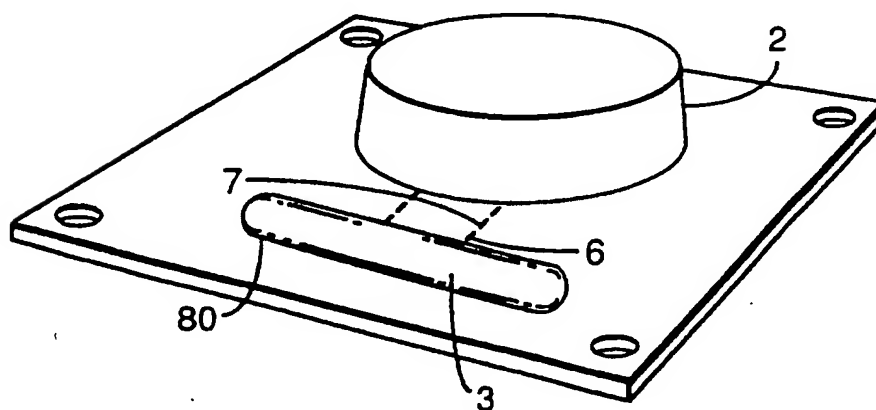


FIG. 8

5/7

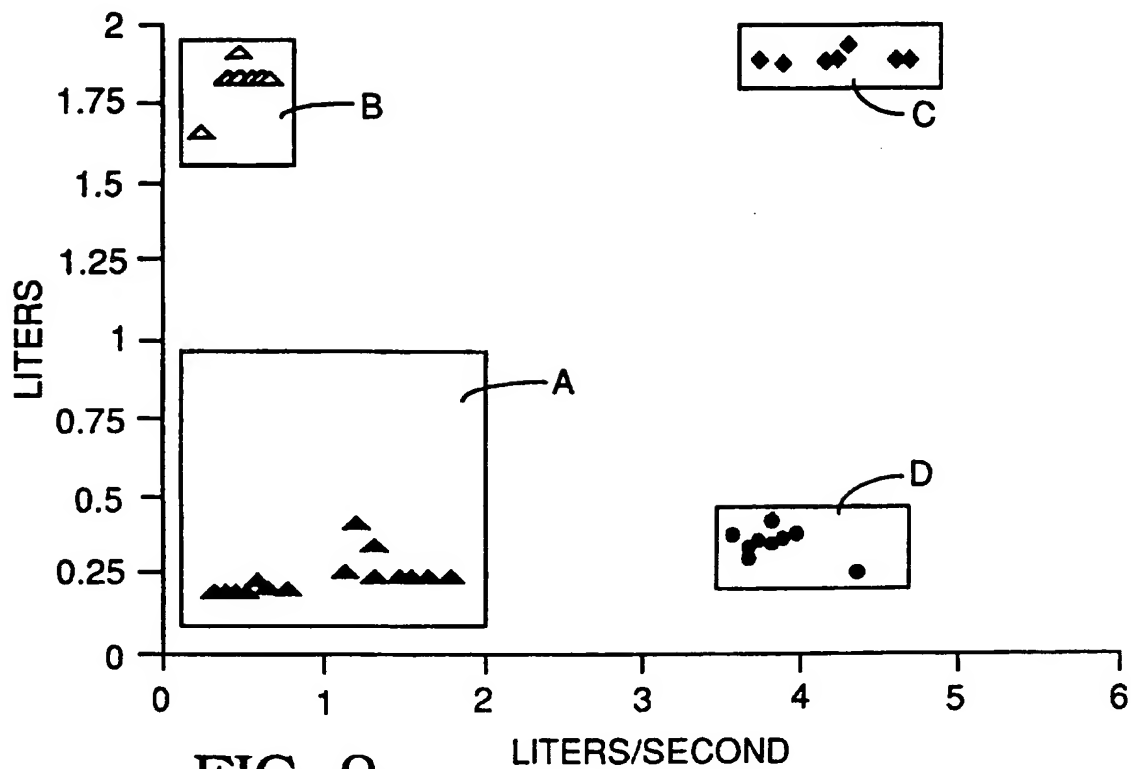


FIG. 9

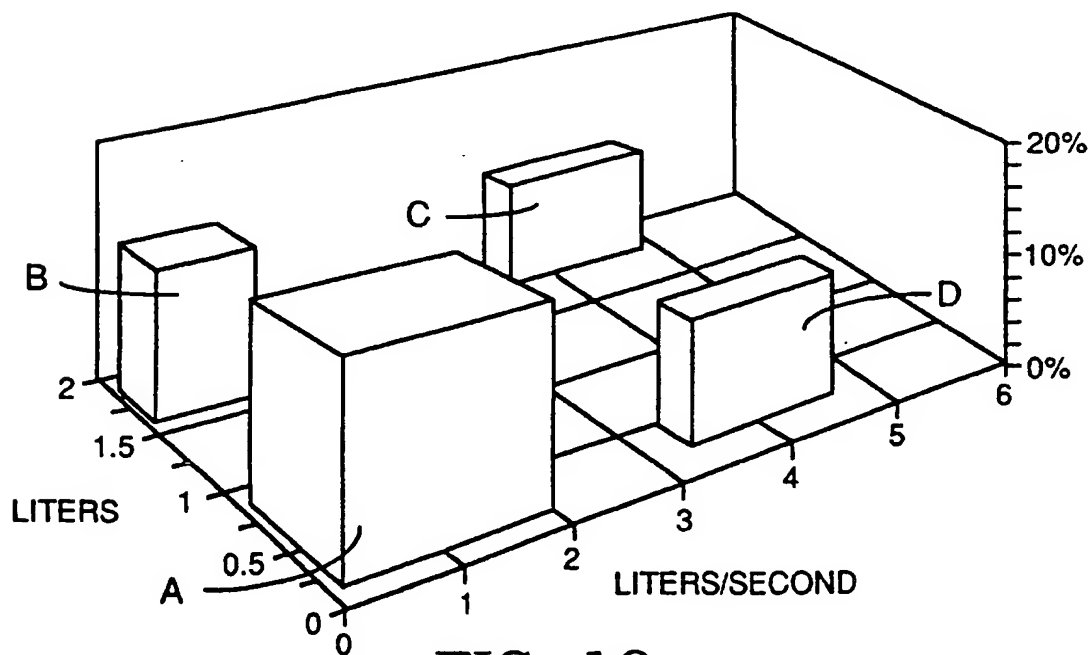


FIG. 10

6/7

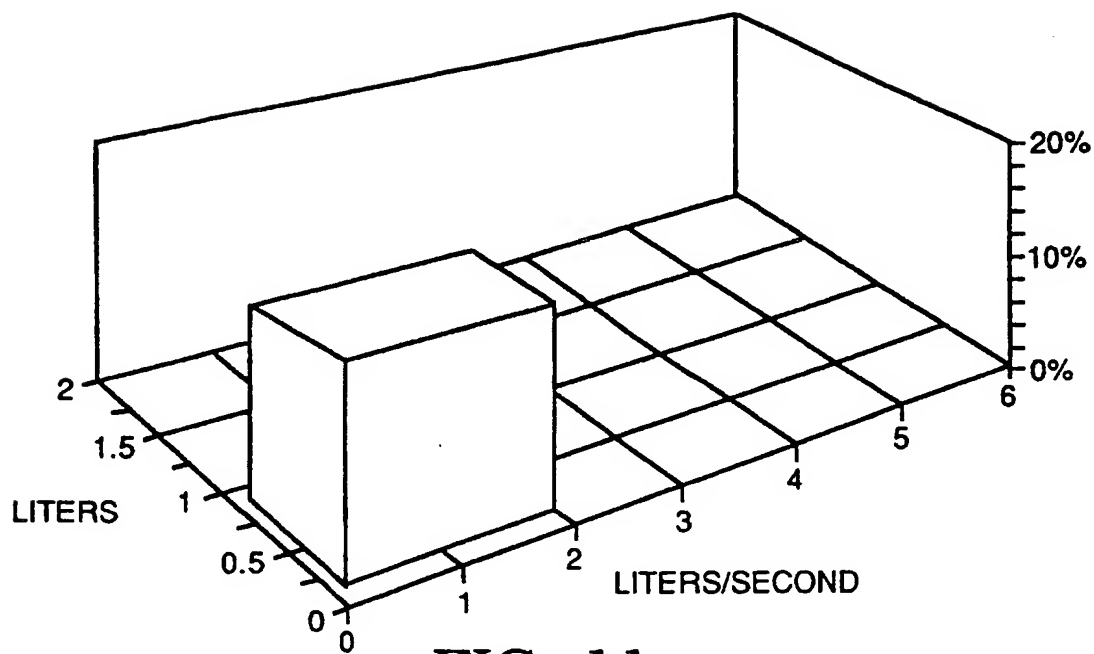


FIG. 11

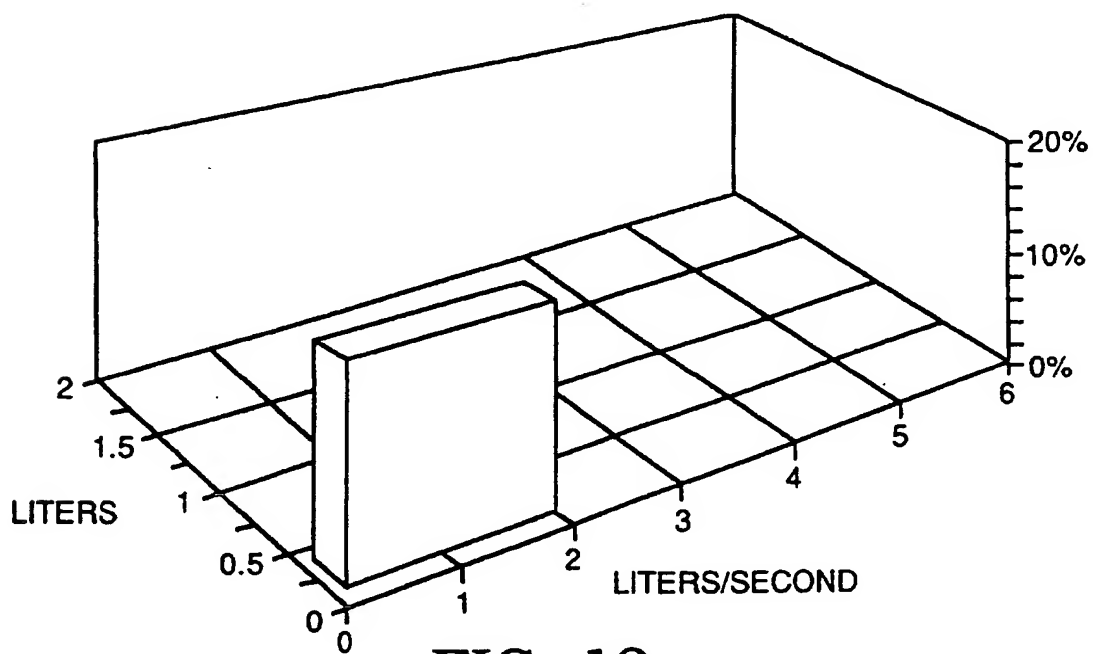


FIG. 12

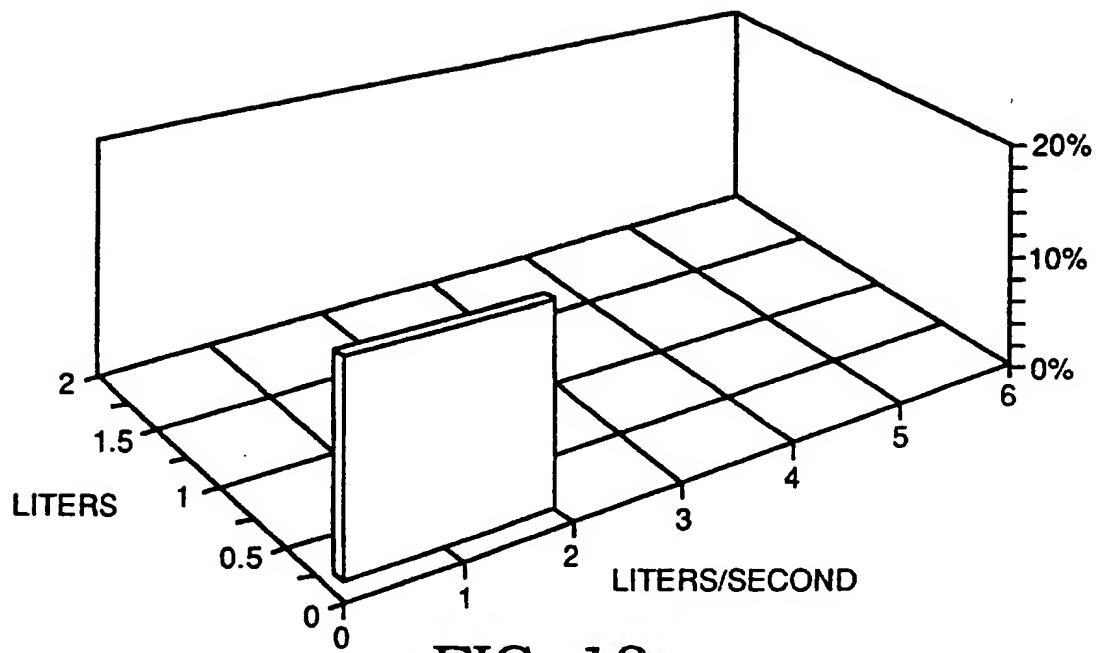


FIG. 13

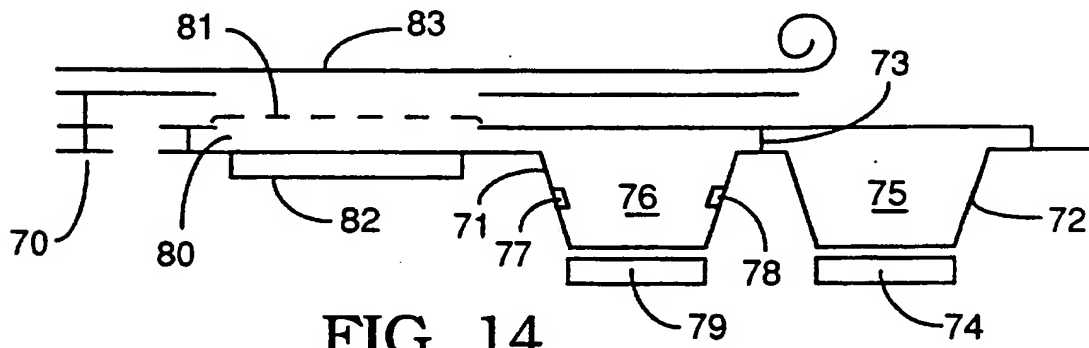


FIG. 14



## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US95/13872**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : : A61M 11/00, 15/00; B65D 47/10

US CL : 128/200.14, 203.12; 222/541.3, 541.4

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : U.S. CL. 128/200.14, 203.12; 222/541.3, 541.4

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
NONEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
NONE**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 3,812,854 (MICHAELS ET AL.) 28 MAY 1974, SEE COL.4, LINES 5-34, COL.5, LINES 21-40, COL.6, LINES 42-58.	1,6-10
Y	US, A, 4,090,642 (BAKER) 23 MAY 1978, SEE FIGS. 6 AND 11.	2,5
Y	US, A, 3,923,057 (CHALON) 02 DECEMBER 1975, SEE FIG.1.	3
Y	US, A, 4,621,632 (BARTELS ET AL.) 11 NOVEMBER 1986, SEE ABSTRACT.	4

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be part of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

17 JANUARY 1996

Date of mailing of the international search report

01 FEB 1996

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer  
AARON J. LEWIS

Telephone No. (703) 308-0716

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**